Predicted Structural Effect of the *HGD* gene missense variants:

The effects of 139 missense variants were assessed in the context of the molecular interactions of the wild-type residue, and mCSM and DUET were used to predict the impact of the variants on protomer and hexamer thermal stability, and mCSM-PPI to predict the effects of the variants on the affinity of the protomers to interact with each other. Predictions in red cells were considered highly destabilizing (ΔΔG <= -1.0 Kcal/mol), in light red marginally destabilizing (-1.0 < ΔΔG <= -0.3 Kcal/mol), in white cells neutral (-0.3 < ΔΔG < 0.3 Kcal/mol), in blue stabilizing variants (ΔΔG >= 0.3 Kcal/mol). The minimum distance from mutated residue to an interface, the active site Fe, and the substrate are given in angstroms. Red cells are within 7 A and likely interacting. *Variant class* is based on mCSM predictions. For each of the 93 mutated residues we indicate also a complement of the *Shannon entropy value* normalized (H10), which reflects residue conservation. The localization in different structural groups within *general HGD monomer structure* is indicated by the presence of the circle under specific category (protomer A was taken as reference): i) interaction protomer-protomer (*interface residues*); ii) solvent accessible *surface residue;* iii) *protomer core* (open and semi-filled circles indicate residues belonging to core 1 (C-terminal domain, bearing active site) or 2 (N-terminal domain)); and iv) protomer active site/pore. Interactions are described in detail, as derived from MD simulation: interacting aminoacid counterpart, interacting chain counterpart (B, C, D, E, F), interaction type (hb=hydrogen bond (with occupancy along the MD if the same is greater than 0.1); vdw= other non-covalent interactions). Multiple interactions are reported as semicolon separated list). DSSP (Dictionary of Secondary Structure of Protein) column reports secondary structure assignment: G=310 helix; H=α helix; I=π helix; T=turn; B=beta bridge; E=extended; S=highly curved; blank=loop.

Variant	Variant	Exon	Variant Class	Destabilise Monomer?	Destabilise Hexamer?	Comments	Dist. to Interface	Dist. to Fe (within protomer)	Dist. to Fe (neighbouring protomer)	Dist. to Substrate (within protomer)	MONOMER		HEXAMER	Shannon entrophy of the residue	position within general HGD monomer structure				
short name	protein change		mCSM proposed effect				(angstroms)	(angstroms)	(angstroms)	(angstroms)	mCSM (ΔΔG Kcal/mol)	protomer_DUET (ΔΔG Kcal/mol)	mCSM-PPI (ΔΔG Kcal/mol)	H.10	Interaction protomer-protomer (Interface residues)	Surface residue	Core protomer	Active site/ Pore	DSSP
E3A	p.(Glu3Ala)	1	unknown	No	No		11.573	36.250	35.361	33.027	-0.059	0.082	-0.355	0.69		●	-	-	
L4S	p.(Leu4Ser)	1	Protomer destabilisation	Yes	No		11.254	36.396	31.566	33.417	-1.243	-1.200	-0.114	0.65		●	-	-	
E13K	p.(Glu13Lys)	2	Hexamer disruption	No	Yes		2.683	35.648	18.326	33.865	0.446	0.700	-1.562	0.51	N12,D,hb,0.71;N12,D,hb,1;P224,D,vdw	-	-	-	
D18N	p.(Asp18Asn)	2	Protomer destabilisation, Hexamer disruption	Yes	Yes		7.825	45.807	25.671	43.374	-1.522	-1.550	-1.004	0.36		-	-	-	
D18Y	p.(Asp18Tyr)	2	Protomer destabilisation, Hexamer disruption	Yes	Yes		7.825	45.807	25.671	43.374	-0.611	-0.671	-0.859	0.36		-	-	-	
L25P	p.(Leu25Pro)	2	Protomer destabilisation, Hexamer disruption	Yes	Mildly		4.255	45.388	20.240	43.331	-1.382	-1.515	-0.694	0.00		●	-	-	S
Q33R	p.(Gln33Arg)	3	Hexamer disruption	No	Yes		2.765	55.868	18.171	54.500	-0.035	0.252	-2.406	0.13	K327,C,hb,0.92;T328,C,vdw;A381,C,vdw;S382,C,vdw;V384,C,hb,0.15;L386,C,vdw	●	-	-	S
Y40S	p.(Tyr40Ser)	3	Protomer destabilisation, Hexamer disruption	Yes	Yes		2.645	47.925	14.731	46.328	-1.344	-1.355	-3.471	0.02	Y334,C,vdw;F378,C,vdw;K431,C,hb,1;K431,C,hb,0.98;H433,C,vdw	-	-	-	E
E42A	p.(Glu42Ala)	3	Protomer destabilisation, Hexamer disruption	Mildly	Yes		2.992	42.320	10.007	40.952	-0.839	-0.883	-2.807	0.00	R336,C,hb,0.23	-	-	-	E
Q43E	p.(Gln43Glu)	3	Hexamer disruption	No	Yes		2.859	40.548	7.531	39.439	-0.004	0.62	-2.96	0.23	N219,D,vdw;D294,C,hb,0.12;Y333,C,hb,0.48;Y334,C,vdw;R336,C,hb,0.69	-	-	-	E
L44P	p.(Leu44Pro)	3	Hexamer disruption	No	Yes		3.458	35.538	9.485	34.179	-1.061	-1.112	-1.182	0.14	R336,C,vdw;M368,C,vdw	-	-	-	E
L44F	p.(Leu44Phe)	3	Protomer destabilisation	Yes	No		3.458	35.538	9.485	34.179	-1.060	-1.182	-0.136	0.14	R336,C,vdw;M368,C,vdw	-	-	-	E
S47L	p.(Ser47Leu)	3	Hexamer disruption	No	Mildly		3.514	32.401	10.310	31.909	-0.308	-0.147	-0.628	0.04	C338,C,vdw	-	-	-	S
R53Q	p.(Arg53Gln)	3	Hexamer disruption	No	Yes		2.836	33.634	18.837	32.838	-0.027	0.245	-3.348	0.00	D212,D,vdw;L210,D,hb,0.88;L213,D, vdw;P211,D,hb,0.97	●	-	-	G
R53W	p.(Arg53Trp)	3	Protomer destabilisation, Hexamer disruption	Mildly	Yes		2.836	33.634	18.837	32.838	-0.492	-0.467	-1.665	0.00	D212,D,vdw;L210,D,hb,0.88;L213,D, vdw;P211,D,hb,0.97	●	-	-	G
K57N	p.(Lys57Asn)	3	Protomer destabilisation	Yes	No		6.026	29.651	12.489	28.633	-1.151	-1.130	-0.227	0.39		●	-	-	
R58S	p.(Arg58Ser)	3	Protomer destabilisation	Yes	No		2.960	35.294	11.770	34.188	-1.689	-1.783	0.359	0.20	A218,D,hb,0.99;N219,D,vdw	●	-	-	E
W60G	p.(Trp60Gly)	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		2.979	40.564	10.039	39.073	-3.793	-3.590	-1.653	0.00	N219,D,vdw;Y333,C,vdw	-	-	-	E
L61P	p.(Leu61Pro)	4	Protomer destabilisation	Yes	No		3.405	39.915	13.572	38.209	-1.947	-2.327	-0.133	0.18		-	-	-	E
Y62N	p.(Tyr62Asn)	4	Protomer destabilisation	Yes	No		4.767	44.961	15.760	43.198	-3.447	-3.618	-0.989	0.00		-	-	-	E
Y62C	p.(Tyr62Cys)	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		4.767	44.961	15.760	43.198	-2.033	-1.975	-1.168	0.00		-	-	-	E

F73L	p.(Phe73Leu)	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		2.777	39.890	14.470	38.696	-1.283	-1.238	-3.516	0.03	N93,C,hb,0.84;T369,C,vdw; N422,C,vdw;H424,C,vdw	-	-	-	
H80Q	p.(His80Gln)	4		No	Mildly		14.726	26.350	30.770	24.562	0.134	0.076	-0.875	0.78		●	-	-	B
E87A	p.(Glu87Ala)	4	Protomer destabilisation, Hexamer disruption	Mildly	Mildly		7.095	25.739	34.091	25.366	-0.496	-0.699	-0.578	0.64		●	-	-	G
P92T	p.(Pro92Thr)	4	Hexamer disruption	No	Yes		3.593	12.369	38.757	12.326	-0.206	0.107	-1.487	0.42	F254,B,vdw;Y249,B,vdw	-	-	-	
W97R	p.(Trp97Arg)	5	Protomer destabilisation	Yes	Yes		10.263	14.408	39.383	12.124	-2.095	-1.980	-0.917	0.01		-	-	-	E
W97G	p.(Trp97Gly)	5	Protomer destabilisation	Yes	No		10.263	14.408	39.383	12.124	-2.582	-2.661	-0.140	0.01		-	-	-	E
W97C	p.(Trp97Cys)	5	Protomer destabilisation	Yes	Mildly		10.125	14.408	39.383	12.124	-1.322	-1.222	-0.765	0.01		-	-	-	E
F100S	p.(Phe100Ser)	5	Protomer destabilisation	Yes	No		16.163	18.981	38.750	15.719	-3.505	-3.599	-0.793	0.53		-	-	-	
G115R	p.(Gly115Arg)	6	Protomer destabilisation	Yes	Yes		19.572	27.442	31.750	24.628	-1.256	-1.124	-2.581	0.13		-	-	-	T
L116P	p.(Leu116Pro)	6	Protomer destabilisation	Yes	Mildly		15.806	26.182	26.510	23.836	-1.569	-1.905	-0.529	0.15		-	-	-	E
C120F	p.(Cys120Phe)	6	Protomer destabilisation	Yes	No		8.712	15.246	30.719	14.194	-0.850	-1.289	-0.371	0.38		-	-	-	E
C120W	p.(Cys120Trp)	6	Protomer destabilisation	Yes	Mildly		8.712	15.246	30.719	14.194	-1.255	-1.488	-0.771	0.38		-	-	-	E
A122D	p.(Ala122Asp)	6	Protomer destabilisation, Hexamer disruption	Yes	Yes		4.578	17.526	27.100	17.585	-0.911	-0.913	-1.048	0.41		-	-	-	E
A122V	p.(Ala122Val)	6	Hexamer disruption	No	Yes		4.578	17.526	27.100	17.585	0.196	0.433	-0.906	0.41		-	-	-	E
G123R	p.(Gly123Arg)	6	Protomer destabilisation, Hexamer disruption	Mildly	Mildly	Positive phi glycine	5.194	20.542	25.832	20.602	-0.655	-0.284	-0.392	0.02		●	-	-	S
G123A	p.(Gly123Ala)	6	Protomer destabilisation, Hexamer disruption	No	Mildly	Positive phi glycine	5.194	20.542	25.832	20.602	-0.227	0.082	-0.408	0.02		●	-	-	S
F136Y	p.(Phe136Tyr)	6	Protomer destabilisation	Yes	Yes		20.230	23.854	31.213	20.932	-0.775	-0.838	-0.732	0.00		-	◑	-	E
L137P	p.(Leu137Pro)	6	Protomer destabilisation	Yes	No		21.989	25.322	34.387	21.856	-1.810	-2.166	0.119	0.65		●	-	-	E
C138Y	p.(Cys138Tyr)	6	Protomer destabilisation	Yes	No		21.827	29.549	33.634	26.185	-1.176	-1.103	-0.685	0.39		-	-	-	E
E143D	p.(Glu143Asp)	6	unknown	No	No		17.854	39.836	29.090	36.991	-0.348	-0.061	-0.195	0.99		●	-	-	
F147S	p.(Phe147Ser)	7	Protomer destabilisation	Yes	No		8.107	29.723	19.783	27.937	-3.393	-3.606	-0.135	0.19		-	◑	-	E
N149K	p.(Asn149Lys)	7	Protomer destabilisation, Hexamer disruption	Mildly	Yes		4.815	26.730	15.669	25.778	-0.618	-0.672	-1.116	0.53		-	-	-	E
S150L	p.(Ser150Leu)	7	Hexamer disruption	No	Yes		3.404	30.937	13.860	30.457	-0.209	-0.195	-1.625	0.34	T367,C,hb,0.57	-	-	-	S
G152R	p.(Gly152Arg)	7	Protomer destabilisation, Hexamer disruption	Yes	Yes	Positive phi glycine	7.208	26.261	17.421	25.463	-1.182	-0.926	-2.141	0.01		-	-	-	E
G152A	p.(Gly152Ala)	7	Protomer destabilisation, Hexamer disruption	Mildly	Mildly	Positive phi glycine	7.208	26.261	17.421	25.463	-0.881	-0.422	-0.743	0.01		-	-	-	E
D153G	p.(Asp153Gly)	7	Protomer destabilisation	Yes	Mildly		7.548	23.170	17.932	22.133	-3.473	-3.742	-0.616	0.01		-	-	-	E
D153N	p.(Asp153Asn)	7	Protomer destabilisation	Yes	No		7.548	23.170	17.932	22.133	-2.637	-2.4	-1.227	0.01		-	-	-	E
V157F	p.(Val157Phe)	7	Protomer destabilisation	Yes	No		17.946	18.636	30.872	15.782	-0.845	-1.304	-1.056	0.12		-	◌	-	E
P158R	p.(Pro158Arg)	8	Protomer destabilisation	Yes	Mildly		18.678	21.880	32.973	18.314	-1.981	-1.724	-0.761	0.12		-	-	-	E
P158L	p.(Pro158Leu)	8	Protomer destabilisation	Yes	Mildly		18.678	21.880	32.973	18.314	-1.217	-0.949	-0.542	0.12		-	-	-	E
Q159H	p.(Gln159His)	8	Protomer destabilisation	Yes	No		20.588	20.902	36.589	16.872	-1.084	-1.176	0.224	0.24		●	-	-	E
G161R	p.(Gly161Arg)	8	Protomer destabilisation	Yes	Yes	Positive phi glycine	20.324	27.695	36.401	23.795	-1.273	-1.325	-1.230	0.02		-	-	-	S

T167I	p.(Thr167Ile)	8	Hexamer disruption	No	Mildly		8.608	33.408	21.210	31.193	0.012	0.208	-0.521	0.00		-		-	E
E168K	p.(Glu168Lys)	8	Hexamer disruption	No	Yes		2.907	37.259	15.112	35.300	0.005	-0.060	-1.308	0.00	R336,C,hb,0.83;R336,C,hb, 0.20;R336,C,hb,0.91	-	-	-	T
E168D	p.(Glu168Asp)	8	Protomer destabilisation, Hexamer disruption	Yes	Mildly		2.907	37.259	15.112	35.300	-1.512	-1.581	-0.528	0.00	R336,C,hb,0.83;R336,C,hb, 0.20;R336,C,hb,0.91	-	-	-	T
F169L	p.(Phe169Leu)	8	Protomer destabilisation	Yes	Mildly		6.069	35.624	16.285	33.812	-1.514	-1.685	-0.668	0.47		-	-	-	T
G170A	p.(Gly170Ala)	8	Protomer destabilisation, Hexamer disruption	Yes	Yes	Positive phi glycine	11.034	36.343	22.777	33.916	-0.757	-0.484	-1.004	0.00		-	-	-	E
G170S	p.(Gly170Ser)	8	Protomer destabilisation, Hexamer disruption	Yes	Yes	Positive phi glycine	11.034	36.343	22.777	33.916	-1.794	-1.632	-1.29	0.00		-	-	-	E
K171N	p.(Lys171Asn)	8	Protomer destabilisation	Yes	Yes		14.003	35.241	26.215	32.531	-1.743	-1.680	-1.317	0.53		●	-	-	E
M172T	p.(Met172Thr)	8	Protomer destabilisation	Yes	No		13.471	30.130	25.493	27.669	-2.606	-2.569	-0.309	0.02		-	-	-	E
E178G	p.(Glu178Gly)	8	Protomer destabilisation	Yes	Yes		10.512	22.679	33.409	19.590	-1.712	-2.022	-1.227	0.30		-	-	-	E
E178D	p.(Glu178Asp)	8	Protomer destabilisation	Yes	Yes		10.512	22.679	33.409	19.590	-1.751	-1.755	-0.976	0.30		-	-	-	E
I179S	p.(Ile179Ser)	8	Protomer destabilisation	Yes	No		13.287	20.165	29.623	17.279	-3.857	-4.121	-0.174	0.03		-		-	E
V181F	p.(Val181Phe)	8	Protomer destabilisation	Yes	Mildly		12.283	23.169	22.713	21.159	-1.412	-1.734	-0.687	0.02		-		-	E
Q183R	p.(Gln183Arg)	8	Protomer destabilisation	Yes	No		6.615	27.558	16.926	26.255	-1.212	-1.261	0.037	0.29		-	-	-	
G185R	p.(Gly185Arg)	9	Protomer destabilisation, Hexamer disruption	Yes	Yes	Positive phi glycine	2.813	31.885	13.471	30.838	-0.922	-0.876	-2.2	0.03	R336,C,hb,0.94	-	-	-	T
M186K	p.(Met186Lys)	9	Protomer destabilisation, Hexamer disruption	Yes	Mildly		4.117	31.767	15.220	30.090	-1.404	-1.518	-0.563	0.11		-	-	-	
R187G	p.(Arg187Gly)	9	Protomer destabilisation	Yes	No		3.389	34.977	13.571	33.255	-1.993	-2.510	-0.310	0.07		-	-	-	
S189I	p.(Ser189Ile)	9	unknown	No	No		11.096	34.418	23.862	31.824	0.657	0.918	-0.057	0.64		-	-	-	E
R197G	p.(Arg197Gly)	9	Protomer destabilisation	Yes	Mildly		22.998	23.195	36.209	19.230	-2.756	-3.087	-0.417	0.08		●	-	-	E
G198D	p.(Gly198Asp)	9	Protomer destabilisation	Yes	Yes		20.822	21.489	33.884	18.274	-2.166	-2.241	-1.041	0.01		-	-	-	E
G205D	p.(Gly205Asp)	9	Protomer destabilisation	Yes	No		5.894	25.554	17.104	25.457	-1.405	-1.550	-0.141	0.33		●	-	-	S
G205V	p.(Gly205Val)	9	Protomer destabilisation	Yes	No	Positive phi glycine	5.894	25.554	17.104	25.457	-0.578	-0.698	-0.278	0.33		●	-	-	S
I216T	p.(Ile216Thr)	9	Protomer destabilisation, Hexamer disruption	Yes	Yes		3.896	18.464	12.905	15.158	-1.052	-1.004	-1.399	0.02	I297,F,vdw;P215,F,vdw	-	-	-	G
G217W	p.(Gly217Trp)	9	Protomer destabilisation, Hexamer disruption	Yes	Mildly	Positive phi glycine	2.912	23.939	12.750	20.926	-1.134	-1.420	-0.687	0.00	N56,D,hb,1;F49,D,vdw;S296, F,hb,1	-	-	-	T
N219S	p.(Asn219Ser)	10	Hexamer disruption	No	Yes		2.859	24.332	11.433	20.411	0.061	0.264	-1.712	0.00	R58,D,vdw;N30,D,hb,0.99;D294, F,hb, 0.99;D294,F,hb,0.98; Q43,D,hb,0.14;T60,D,vdw	-	-	-	S
G220V	p.(Gly220Val)	10	Hexamer disruption	No	Yes		4.686	22.052	15.966	18.210	-0.066	-0.359	-1.055	0.16		-	-	-	
A222D	p.(Ala222Asp)	10	Protomer destabilisation	Yes	No		4.184	20.786	21.503	17.603	-2.053	-2.272	-0.731	0.02		-	-	-	S
R225P	p.(Arg225Pro)	10	Hexamer disruption	No	Yes		3.004	28.991	19.555	26.111	0.253	0.289	-2.216	0.03	N30,D,vdw;Q29,D,vdw;H269,D, vdw;P26,D,hb,0.98;S15,D,vdw	●	-	-	G
R225H	p.(Arg225His)	10	Hexamer disruption	No	Yes		3.004	28.991	19.555	26.111	-0.723	-0.682	-1.907	0.03	N30,D,vdw;Q29,D,vdw;H269,D,v dw; P26,D,hb,0.98;S15,D,vdw	●	-	-	G
R225L	p.(Arg225Leu)	10	Hexamer disruption	No	Yes		3.004	28.991	19.555	26.111	0.377	0.462	-2.236	0.03	N30,D,vdw;Q29,D,vdw;H269,D,v dw; P26,D,hb,0.98;S15,D,vdw	●	-	-	G

F227S	p.(Phe227Ser)	10	Protomer destabilisation	Yes	No		7.218	22.905	25.060	20.444	-2.801	-3.053	-0.018	0.00		-	-	-	E
F227L	p.(Phe227Leu)	10	Unknown	No	No		7.218	22.905	25.060	20.444	-0.606	-0.87	-0.548	0.00		-	-	-	E
P230T	p.(Pro230Thr)	10	Protomer destabilisation	Yes	No		12.074	33.264	24.181	30.804	-2.416	-2.165	-0.268	0.00		-	-	-	E
P230S	p.(Pro230Ser)	10	Protomer destabilisation	Yes	No		12.074	33.264	24.181	30.804	-2.830	-2.724	-0.093	0.00		-	-	-	E
V245F	p.(Val245Phe)	10	Protomer destabilisation	Yes	No		7.354	38.938	17.666	37.217	-1.486	-1.797	-0.431	0.04		-	-	-	E
K248E	p.(Lys248Glu)	10	Protomer destabilisation	Yes	No		6.628	26.883	17.333	26.163	-1.903	-1.955	-0.146	0.00		-	-	-	E
K248R	p.(Lys248Arg)	10	Protomer destabilisation, Hexamer disruption	Yes	Yes		6.628	26.883	17.333	26.163	-1.465	-1.357	-1.077	0.00		-	-	-	E
G251D	p.(Gly251Asp)	10	Protomer destabilisation	Yes	Yes	Positive phi glycine	6.039	29.538	20.507	28.955	-2.303	-2.640	-1.518	0.10		-	-	-	T
Q258P	p.(Gln258Pro)	10	Protomer destabilisation	Mildly	No		7.087	44.113	17.503	42.529	-0.428	-0.712	-0.254	0.54		-	-	-	E
F263L	p.(Phe263Leu)	11	Protomer destabilisation	Yes	No		8.556	38.064	20.715	35.981	-2.112	-2.34	-0.788	0.35		-	-	-	
N264S	p.(Asn264Ser)	11	Protomer destabilisation	Yes	No		7.110	44.118	18.361	42.094	-1.967	-2.24	-0.413	0.30		-	-	-	
A267V	p.(Ala267Val)	11	Protomer destabilisation, Hexamer disruption	Mildly	Mildly		8.111	43.953	18.589	41.933	-0.58	-0.297	-0.446	0.02		-	-	-	E
H269R	p.(His269Arg)	11	Protomer destabilisation, Hexamer disruption	Mildly	Yes		3.360	39.892	16.346	38.168	-0.822	-0.763	-2.379	0.14	R225,D,vdw	-	-	-	E
G270R	p.(Gly270Arg)	11	Protomer destabilisation, Hexamer disruption	Yes	Yes		6.109	36.522	17.370	34.754	-1.094	-0.838	-2.435	0.00		-	-	-	E
P274L	p.(Pro274Leu)	11	Protomer destabilisation	Mildly	No		9.123	30.037	20.338	27.843	-0.650	-0.465	-0.317	0.00		-	◑	-	
K276N	p.(Lys276Asn)	11	Protomer destabilisation	Yes	No		11.345	26.405	27.468	23.615	-2.207	-2.241	-0.251	0.25		●	-	-	E
N278D	p.(Asn278Asp)	11	Protomer destabilisation	Yes	No		8.037	23.483	27.901	20.007	-1.336	-1.173	-0.077	0.36		●	-	-	E
D291E	p.(Asp291Glu)	11	Hexamer disruption	No	Yes		2.799	14.926	26.989	9.792	-0.483	-0.163	-2.705	0.00	N30,B,hb,0.82;N30,B,hb,0.98; N31,B,hb,0.35;Q29,B,vdw; M283,F,vdw	-	-	-	S
H292R	p.(His292Arg)	11	Protomer destabilisation, Hexamer disruption, Active site disruption	Mildly	Yes	Interacts with substrate	3.383	8.784	27.682	2.910	-0.815	-0.731	-1.857	0.00	N31,B,vdw;M283,F,vdw	●	-	●	
V300G	p.(Val300Gly)	12	Protomer destabilisation	Yes	Mildly		6.349	15.521	25.982	13.244	-2.166	-2.632	-0.417	0.00		-	-	-	E
S305F	p.(Ser305Phe)	12	Protomer destabilisation, Hexamer disruption	Yes	Mildly		3.333	18.816	25.843	18.869	-0.851	-0.922	-0.666	0.17	R307,C,vdw	-	-	-	
G309V	p.(Gly309Val)	12	Hexamer disruption	No	Yes	Positive phi glycine	2.665	15.047	28.854	14.796	-0.388	-0.170	-1.110	0.06	C51,B,vdw;T50,B,hb,0.99	●	-	-	T
V316I	p.(Val316Ile)	12	Unknown	No	No		7.704	9.977	29.853	7.329	-0.625	-0.374	-0.539	0.11		-	-	-	E
R321P	p.(Arg321Pro)	12	Protomer destabilisation, Active site disruption	Yes	No	Active site residue	3.624	12.769	25.983	5.788	-0.605	-1.073	-0.255	0.00	A289,F,vdw	●	-	●	E
W322R	p.(Trp322Arg)	12	Hexamer disruption	No	Yes		2.920	18.889	24.366	11.652	-0.393	-0.379	-3.559	0.06	D326,F,hb,0.16;P388,F,vdw; V288,F,hb,0.99;V324,F,hb,0.25	●	-	-	E
F329C	p.(Phe329Cys)	12	Protomer destabilisation	Yes	Yes		3.073	12.082	32.682	8.325	-1.155	-1.003	-1.871	0.00	N31,B,vdw;P32,B,vdw	-	-	-	
R330S	p.(Arg330Ser)	12	Protomer destabilisation, Active site disruption	Yes	No	Active site residue	5.894	12.360	29.637	5.888	-1.361	-1.649	-0.096	0.00		●	-	●	

P332R	**p.(Pro332Arg)**	12	Protomer destabilization Active site disruption	Mildly	No	Loss of backbone rigidity- altering substrate binding and metal coordination	6.803	6.903	34.630	3.395	-0.817	-0.608	-0.205	0.00		●	-	●	
R336K	**p.(Arg336Lys)**	12	Hexamer & Active site disruption	No	Yes		2.813	6.059	37.312	7.187	0.033	0.303	-1.53	0.00	R63,B,vdw;Q43,B,hb,0.69;E168,B,hb,0.83;E168,B,hb,0.2;E168,B,hb,0.91;E42,B,hb,0.23;G185,B,hb,0.94;L44,B,vdw;S45,B,hb,0.99;S67,B,vdw	-	-	-	
R336T	**p.(Arg336Thr)**	12	Hexamer disruption, Active site disruption	No	Yes		2.690	6.750	38.270	7.070	0.418	0.506	-1.589	0.00	R63,B,vdw;Q43,B,hb,0.69;E168,B,hb,0.83;E168,B,hb,0.2;E168,B,hb,0.91;E42,B,hb,0.23;G185,B,hb,0.94;L44,B,vdw;S45,B,hb,0.99;S67,B,vdw	-	-	-	
N337D	**p.(Asn337Asp)**	13	Protomer destabilisation, Hexamer disruption, Active site disruption	Yes	Yes	Active site residue	3.548	4.604	35.766	4.705	-1.194	-1.205	-1.772	0.00	S45,B,vdw	-	-	-	
L345R	**p.(Leu345Arg)**	13	Protomer destabilisation	Yes	No		17.237	15.041	38.576	10.943	-1.379	-1.052	-1.206	0.04		-	-	-	E
I346T	**p.(Ile346Thr)**	13	Protomer destabilisation	Yes	No		15.430	17.453	35.736	13.356	-2.822	-3.019	-0.176	0.00		-	-	-	
R347P	**p.(Arg347Pro)**	13	Active site disruption	Mildly	No	Alters conformation of loop at active site opening	11.500	18.700	35.200	13.700	0.119	-0.301	0.119	0.83		●	-	-	
Y350C	**p.(Tyr350Cys)**	13	Active site disruption	No	No	Alters conformation of loop at active site opening	11.640	10.460	29.890	14.400	0.195	-0.240	-0.087	0.00		-	-	●	
K353Q	**p.(Lys353Gln)**	13	Active site disruption	No	No	Active site residue	7.656	9.576	40.282	5.611	0.320	0.357	0.121	0.00		-	-	●	
P359L	**p.(Pro359Leu)**	13	Active site disruption	Mildly	Mildly	Important kink in loop at active site	20.860	20.085	42.815	15.740	-0.733	-0.688	-0.675	0.06		●	-	-	T
G360R	**p.(Gly360Arg)**	13	Protomer destabilisation	Yes	Yes	Positive phi glycine	19.970	18.762	42.471	14.548	-0.878	-1.029	-1.819	0.00		-	-	-	T
G360A	**p.(Gly360Ala)**	13	Protomer destabilisation	Yes	Mildly	Positive phi glycine	19.970	18.762	42.471	14.548	-0.675	-0.911	-0.501	0.00		-	-	-	T
G361R	**p.(Gly361Arg)**	13	Protomer destabilisation	Mildly	Yes		17.385	15.933	40.339	12.097	-0.560	-0.448	-2.173	0.03		-	-	-	
G362E	**p.(Gly362Glu)**	13	Protomer destabilisation	Yes	Yes		14.145	13.367	41.054	9.943	-1.011	-1.002	-1.143	0.14		-	-	-	E
M368V	**p.(Met368Val)**	13	Hexamer disruption	No	Yes		3.259	9.001	33.799	9.163	-0.510	-0.267	-1.253	0.10	L44,B,vdw;Y148,B,vdw	-	-	-	T
H371R	**p.(His371Arg)**	13	Active site disruption, Hexamer disruption	Mildly	Yes	Coordinates active Fe	3.379	2.323	38.809	2.435	-0.851	-0.824	-1.712	0.00		-	-	◌	B
G372R	**p.(Gly372Arg)**	13	Active site disruption	No	No		4.013	6.783	40.515	6.478	-0.869	-0.804	-0.632	0.00		●	-	●	
P373L	**p.(Pro373Leu)**	13	Active site disruption	No	Mildly	Roof of active site	5.073	8.934	39.488	7.781	-0.472	-0.394	-0.610	0.02		-	-	●	
D374H	**p.(Asp374His)**	13	Active site disruption	No	No	Roof of active site	7.024	12.227	43.170	10.699	-0.025	-0.079	0.837	0.01		●	-	●	
E401Q	**p.(Glu401Gln)**	14	Active site disruption, Hexamer disruption	No	Yes	Active site residue	4.293	6.648	32.045	6.656	-0.048	0.168	-0.897	0.00		-	-	●	E