

Predicted Structural Effect of the *HGD* gene Missense Variants:

The effects of 97 missense variants were assessed in the context of the molecular interactions of the wild-type residue, and mCSM (Pires et al. 2014a) and DUET (Pires et al. 2014b) were used to predict the impact of the variants on protomer and hexamer thermal stability, and mCSM-PPI (Pires et al. 2014a) 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 destabilising ($\Delta\Delta G \leq -1.0$ Kcal/mol), in light red marginally destabilizing ($-1.0 < \Delta\Delta G \leq -0.3$ Kcal/mol), in white cells neutral ($-0.3 < \Delta\Delta G < 0.3$ Kcal/mol), in blue stabilising mutations ($\Delta\Delta G \geq 0.3$ 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 Å and likely interacting.

Variant brief name	Exon	Mutation Class	Destabilise Monomer?	Destabilise Hexamer?	Comments	MONOMER		HEXAMER	Dist. to Interface (angstroms)	Dist. to Fe (within protomer) (angstroms)	Dist. to Fe (neighbouring protomer) (angstroms)	Dist. to Substrate (within protomer) (angstroms)
						mCSM ($\Delta\Delta G$ Kcal/mol)	monomer_DUET ($\Delta\Delta G$ Kcal/mol)	mCSM-PPI ($\Delta\Delta G$ Kcal/mol)				
E3A	1	unknown	No	No		-0.059	0.082	-0.355	11.573	36.250	35.361	33.027
L4S	1	Protomer destabilisation	Yes	No		-1.243	-1.200	-0.114	11.254	36.396	31.566	33.417
E13K	2	Hexamer disruption	No	Yes		0.446	0.700	-1.562	2.683	35.648	18.326	33.865
D18N	2	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.522	-1.550	-1.004	7.825	45.807	25.671	43.374
L25P	2	Protomer destabilisation, Hexamer disruption	Yes	Mildly		-1.382	-1.515	-0.694	4.255	45.388	20.240	43.331
Q33R	3	Hexamer disruption	No	Yes		-0.035	0.252	-2.406	2.765	55.868	18.171	54.500
Y40S	3	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.344	-1.355	-3.471	2.645	47.925	14.731	46.328
E42A	3	Protomer destabilisation, Hexamer disruption	Mildly	Yes		-0.839	-0.883	-2.807	2.992	42.320	10.007	40.952
L44F	3	Protomer destabilisation	Yes	No		-1.060	-1.182	-0.136	3.458	35.538	9.485	34.179
S47L	3	Hexamer disruption	No	Mildly		-0.308	-0.147	-0.628	3.514	32.401	10.310	31.909
R53Q	3	Hexamer disruption	No	Yes		-0.027	0.245	-3.348	2.836	33.634	18.837	32.838
R53W	3	Protomer destabilisation, Hexamer disruption	Mildly	Yes		-0.492	-0.467	-1.665	2.836	33.634	18.837	32.838
K57N	3	Protomer destabilisation	Yes	No		-1.151	-1.130	-0.227	6.026	29.651	12.489	28.633
W60G	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		-3.793	-3.590	-1.653	2.979	40.564	10.039	39.073
L61P	4	Protomer destabilisation	Yes	No		-1.947	-2.327	-0.133	3.405	39.915	13.572	38.209
Y62C	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		-2.033	-1.975	-1.168	4.767	44.961	15.760	43.198
F73L	4	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.283	-1.238	-3.516	2.777	39.890	14.470	38.696
H80Q	4		No	Mildly		0.134	0.076	-0.875	14.726	26.350	30.770	24.562
E87A	4	Protomer destabilisation, Hexamer disruption	Mildly	Mildly		-0.496	-0.699	-0.578	7.095	25.739	34.091	25.366
P92T	4	Hexamer disruption	No	Yes		-0.206	0.107	-1.487	3.593	12.369	38.757	12.326
W97R	5	Protomer destabilisation	Yes	Yes		-2.095	-1.980	-0.917	10.263	14.408	39.383	12.124
W97G	5	Protomer destabilisation	Yes	No		-2.582	-2.661	-0.140	10.263	14.408	39.383	12.124
G115R	6	Protomer destabilisation	Yes	Yes		-1.256	-1.124	-2.581	19.572	27.442	31.750	24.628
L116P	6	Protomer destabilisation	Yes	Mildly		-1.569	-1.905	-0.529	15.806	26.182	26.510	23.836
C120F	6	Protomer destabilisation	Yes	No		-0.850	-1.289	-0.371	8.712	15.246	30.719	14.194
C120W	6	Protomer destabilisation	Yes	Mildly		-1.255	-1.488	-0.771	8.712	15.246	30.719	14.194
A122D	6	Protomer destabilisation, Hexamer disruption	Yes	Yes		-0.911	-0.913	-1.048	4.578	17.526	27.100	17.585
A122V	6	Hexamer disruption	No	Yes		0.196	0.433	-0.906	4.578	17.526	27.100	17.585

G123R	6	Protomer destabilisation, Hexamer disruption	Mildly	Mildly	Positive phi glycine	-0.655	-0.284	-0.392	5.194	20.542	25.832	20.602
G123A	6	Protomer destabilisation, Hexamer disruption	No	Mildly	Positive phi glycine	-0.227	0.082	-0.408	5.194	20.542	25.832	20.602
F136Y	6	Protomer destabilisation	Yes	Yes		-0.775	-0.838	-0.732	20.230	23.854	31.213	20.932
L137P	6	Protomer destabilisation	Yes	No		-1.810	-2.166	0.119	21.989	25.322	34.387	21.856
E143D	6	unknown	No	No		-0.348	-0.061	-0.195	17.854	39.836	29.090	36.991
F147S	7	Protomer destabilisation	Yes	No		-3.393	-3.606	-0.135	8.107	29.723	19.783	27.937
N149K	7	Protomer destabilisation, Hexamer disruption	Mildly	Yes		-0.618	-0.672	-1.116	4.815	26.730	15.669	25.778
G152A	7	Protomer destabilisation, Hexamer disruption	Mildly	Mildly	Positive phi glycine	-0.881	-0.422	-0.743	7.208	26.261	17.421	25.463
D153G	7	Protomer destabilisation	Yes	Mildly		-3.473	-3.742	-0.616	7.548	23.170	17.932	22.133
P158R	8	Protomer destabilisation	Yes	Mildly		-1.981	-1.724	-0.761	18.678	21.880	32.973	18.314
P158L	8	Protomer destabilisation	Yes	Mildly		-1.217	-0.949	-0.542	18.678	21.880	32.973	18.314
Q159H	8	Protomer destabilisation	Yes	No		-1.084	-1.176	0.224	20.588	20.902	36.589	16.872
G161R	8	Protomer destabilisation	Yes	Yes	Positive phi glycine	-1.273	-1.325	-1.230	20.324	27.695	36.401	23.795
T167I	8	Hexamer disruption	No	Mildly		0.012	0.208	-0.521	8.608	33.408	21.210	31.193
E168K	8	Hexamer disruption	No	Yes		0.005	-0.060	-1.308	2.907	37.259	15.112	35.300
E168D	8	Protomer destabilisation, Hexamer disruption	Yes	Mildly		-1.512	-1.581	-0.528	2.907	37.259	15.112	35.300
F169L	8	Protomer destabilisation	Yes	Mildly		-1.514	-1.685	-0.668	6.069	35.624	16.285	33.812
K171N	8	Protomer destabilisation	Yes	Yes		-1.743	-1.680	-1.317	14.003	35.241	26.215	32.531
M172T	8	Protomer destabilisation	Yes	No		-2.606	-2.569	-0.309	13.471	30.130	25.493	27.669
E178G	8	Protomer destabilisation	Yes	Yes		-1.712	-2.022	-1.227	10.512	22.679	33.409	19.590
E178D	8	Protomer destabilisation	Yes	Yes		-1.751	-1.755	-0.976	10.512	22.679	33.409	19.590
V181F	8	Protomer destabilisation	Yes	Mildly		-1.412	-1.734	-0.687	12.283	23.169	22.713	21.159
Q183R	8	Protomer destabilisation	Yes	No		-1.212	-1.261	0.037	6.615	27.558	16.926	26.255
M186K	9	Protomer destabilisation, Hexamer disruption	Yes	Mildly		-1.404	-1.518	-0.563	4.117	31.767	15.220	30.090
R187G	9	Protomer destabilisation	Yes	No		-1.993	-2.510	-0.310	3.389	34.977	13.571	33.255
S189I	9	unknown	No	No		0.657	0.918	-0.057	11.096	34.418	23.862	31.824
R197G	9	Protomer destabilisation	Yes	Mildly		-2.756	-3.087	-0.417	22.998	23.195	36.209	19.230
G198D	9	Protomer destabilisation	Yes	Yes		-2.166	-2.241	-1.041	20.822	21.489	33.884	18.274
G205D	9	Protomer destabilisation	Yes	No		-1.405	-1.550	-0.141	5.894	25.554	17.104	25.457
I216T	9	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.052	-1.004	-1.399	3.896	18.464	12.905	15.158
G217W	9	Protomer destabilisation, Hexamer disruption	Yes	Mildly	Positive phi glycine	-1.134	-1.420	-0.687	2.912	23.939	12.750	20.926
N219S	10	Hexamer disruption	No	Yes		0.061	0.264	-1.712	2.859	24.332	11.433	20.411
R225P	10	Hexamer disruption	No	Yes		0.253	0.289	-2.216	3.004	28.991	19.555	26.111
R225H	10	Hexamer disruption	No	Yes		-0.723	-0.682	-1.907	3.004	28.991	19.555	26.111
R225L	10	Hexamer disruption	No	Yes		0.377	0.462	-2.236	3.004	28.991	19.555	26.111
F227S	10	Protomer destabilisation	Yes	No		-2.801	-3.053	-0.018	7.218	22.905	25.060	20.444
P230T	10	Protomer destabilisation	Yes	No		-2.416	-2.165	-0.268	12.074	33.264	24.181	30.804
P230S	10	Protomer destabilisation	Yes	No		-2.830	-2.724	-0.093	12.074	33.264	24.181	30.804
V245F	10	Protomer destabilisation	Yes	No		-1.486	-1.797	-0.431	7.354	38.938	17.666	37.217
K248E	10	Protomer destabilisation	Yes	No		-1.903	-1.955	-0.146	6.628	26.883	17.333	26.163
K248R	10	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.465	-1.357	-1.077	6.628	26.883	17.333	26.163
G251D	10	Protomer destabilisation	Yes	Yes	Positive phi glycine	-2.303	-2.640	-1.518	6.039	29.538	20.507	28.955
Q258P	10	Protomer destabilisation	Mildly	No		-0.428	-0.712	-0.254	7.087	44.113	17.503	42.529

H269R	11	Protomer destabilisation, Hexamer disruption	Mildly	Yes		-0.822	-0.763	-2.379	3.360	39.892	16.346	38.168
G270R	11	Protomer destabilisation, Hexamer disruption	Yes	Yes		-1.094	-0.838	-2.435	6.109	36.522	17.370	34.754
P274L	11	Protomer destabilisation	Mildly	No		-0.650	-0.465	-0.317	9.123	30.037	20.338	27.843
K276N	11	Protomer destabilisation	Yes	No		-2.207	-2.241	-0.251	11.345	26.405	27.468	23.615
N278D	11	Protomer destabilisation	Yes	No		-1.336	-1.173	-0.077	8.037	23.483	27.901	20.007
D291E	11	Hexamer disruption	No	Yes		-0.483	-0.163	-2.705	2.799	14.926	26.989	9.792
H292R	11	Protomer destabilisation, Hexamer disruption, Active site disruption	Mildly	Yes	Interacts with substrate	-0.815	-0.731	-1.857	3.383	8.784	27.682	2.910
V300G	12	Protomer destabilisation	Yes	Mildly		-2.166	-2.632	-0.417	6.349	15.521	25.982	13.244
S305F	12	Protomer destabilisation, Hexamer disruption	Yes	Mildly		-0.851	-0.922	-0.666	3.333	18.816	25.843	18.869
G309V	12	Hexamer disruption	No	Yes	Positive phi glycine	-0.388	-0.170	-1.110	2.665	15.047	28.854	14.796
R321P	12	Protomer destabilisation, Active site disruption	Yes	No	Active site residue	-0.605	-1.073	-0.255	3.624	12.769	25.983	5.788
W322R	12	Hexamer disruption	No	Yes		-0.393	-0.379	-3.559	2.920	18.889	24.366	11.652
F329C	12	Protomer destabilisation	Yes	Yes		-1.155	-1.003	-1.871	3.073	12.082	32.682	8.325
R330S	12	Protomer destabilisation, Active site disruption	Yes	No	Active site residue	-1.361	-1.649	-0.096	5.894	12.360	29.637	5.888
N337D	13	Protomer destabilisation, Hexamer disruption, Active site disruption	Yes	Yes	Active site residue	-1.194	-1.205	-1.772	3.548	4.604	35.766	4.705
K353Q	13	Active site disruption	No	No	Active site residue	0.320	0.357	0.121	7.656	9.576	40.282	5.611
P359L	13	Active site disruption	Mildly	Mildly	Important kink in loop at active site	-0.733	-0.688	-0.675	20.860	20.085	42.815	15.740
G360R	13	Protomer destabilisation	Yes	Yes	Positive phi glycine	-0.878	-1.029	-1.819	19.970	18.762	42.471	14.548
G360A	13	Protomer destabilisation	Yes	Mildly	Positive phi glycine	-0.675	-0.911	-0.501	19.970	18.762	42.471	14.548
G361R	13	Protomer destabilisation	Mildly	Yes		-0.560	-0.448	-2.173	17.385	15.933	40.339	12.097
G362E	13	Protomer destabilisation	Yes	Yes		-1.011	-1.002	-1.143	14.145	13.367	41.054	9.943
M368V	13	Hexamer disruption	No	Yes		-0.510	-0.267	-1.253	3.259	9.001	33.799	9.163
H371R	13	Active site disruption, Hexamer disruption	Mildly	Yes	Coordinates active Fe	-0.851	-0.824	-1.712	3.379	2.323	38.809	2.435
P373L	13	Active site disruption	No	Mildly	Roof of active site	-0.472	-0.394	-0.610	5.073	8.934	39.488	7.781
D374H	13	Active site disruption	No	No	Roof of active site	-0.025	-0.079	0.837	7.024	12.227	43.170	10.699
E401Q	14	Active site disruption, Hexamer disruption	No	Yes	Active site residue	-0.048	0.168	-0.897	4.293	6.648	32.045	6.656