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## Supplementary Material

2 **Supplementary Table ST1:** The dimensions and the narrowest cross-section (area) of the three access  
 3 channels measured near the surface of the 3D structure of the protein. The homology model for each  
 4 sequence is provided in a supplementary file named as listed in the last column of this Table. % $\Delta$  refers  
 5 to percentage change of the cross-sectional area of the channel as compared to that of the WT channel.  
 6 The WT and S315T structures, 2CCA.pdb and 2CCD.pdb respectively, were obtained from the RCSB Protein  
 7 Data Bank ([www.rcsb.org](http://www.rcsb.org)).

	Channel 1				Channel 2				Channel 3				File Name
	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	
<b>WT</b>	9.20	9.22	66.62	0.00	9.28	8.73	63.63	0.00	7.49	6.69	39.35	0.00	
<b>S315T</b>	9.31	8.85	64.71	-2.87	8.94	8.58	60.24	-5.32	7.31	6.71	38.52	-2.11	
<b>Novel mutations reported by Torres et al. [4]</b>													
<b>Y64S</b>	7.71	8.83	53.47	-19.74	8.61	7.45	50.38	-20.82	6.29	6.41	31.67	-19.54	Y64S.pdb
<b>Y95C</b>	8.84	6.91	47.98	-27.99	8.25	7.78	50.41	-20.77	5.29	5.25	21.81	-44.57	Y95C.pdb
<b>P131T</b>	8.8	7.95	54.95	-17.52	8.33	7.36	48.15	-24.32	6.36	6.44	32.17	-18.26	P131T.pdb
<b>A139P</b>	10.00	7.17	56.31	-15.47	7.33	7.24	41.68	-34.49	5.16	5.22	21.15	-46.25	A139P.pdb
<b>D142G</b>	8.91	7.02	49.13	-26.26	7.51	8.79	51.85	-18.52	5.42	5.31	22.60	-42.56	D142G.pdb
<b>A162V</b>	7.94	8.24	51.39	-22.87	7.05	7.30	40.42	-36.47	6.26	6.44	31.66	-19.55	A162V.pdb
<b>G269D</b>	8.69	8.15	55.62	-16.51	7.06	7.21	39.98	-37.17	6.22	6.28	30.68	-22.05	G269D.pdb
<b>T306P</b>	8.79	7.80	53.85	-19.17	8.63	7.70	52.19	-17.98	5.37	5.51	23.24	-40.95	T306P.pdb
<b>R385W</b>	9.04	8.25	58.57	-12.08	8.17	7.28	46.71	-26.58	6.61	6.75	35.04	-10.96	R385W.pdb
<b>D387G</b>	8.70	7.56	51.66	-22.46	8.38	7.41	48.77	-23.35	5.78	5.89	26.74	-32.06	D387G.pdb
<b>T394M</b>	8.63	8.21	55.65	-16.47	7.60	7.16	42.74	-32.83	5.68	5.85	26.10	-33.69	T394M.pdb
<b>Q439P</b>	9.56	8.12	60.97	-8.48	7.20	7.17	40.55	-36.28	6.12	5.90	28.36	-27.94	Q439P.pdb
<b>F483L</b>	8.85	7.27	50.53	-24.15	8.12	7.40	47.19	-25.83	5.23	5.98	24.56	-37.58	F483L.pdb
<b>A541D</b>	9.25	7.02	51.00	-23.45	7.19	7.21	40.71	-36.01	5.77	5.63	25.51	-35.17	A541D.pdb
<b>Control Mutations</b>													
<b>A110V</b>	9.32	9.31	68.15	+2.29	9.10	8.93	63.82	+0.31	7.34	6.76	38.97	-0.98	A110V.pdb
<b>L499M</b>	9.24	9.31	67.56	+1.42	8.94	9.07	63.68	+0.09	7.47	6.85	40.19	+2.12	L499M.pdb
<b>L587P</b>	9.00	9.13	64.54	-3.13	9.11	9.32	66.68	+4.80	7.15	6.85	38.47	-2.26	L587P.pdb
<b>R463L</b>	9.17	9.17	66.04	-0.87	8.91	9.17	64.17	+0.85	7.54	6.94	41.10	+4.43	R463L.pdb
<b>S316G</b>	8.89	9.04	63.12	-5.26	8.99	9.36	66.09	+3.87	7.37	6.95	40.23	+2.22	S316G.pdb

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9 **Supplementary Table ST2:** The dimensions and the opening (area) of the three access channels  
 10 measured near the heme at the catalytic center of the protein. The homology model for each sequence is  
 11 provided in a supplementary file named as listed in the last column of this Table. % $\Delta$  refers to percentage  
 12 change of the cross-sectional area of the channel as compared to that of the WT channel. The WT and  
 13 S315T structures, 2CCA.pdb and 2CCD.pdb respectively, were obtained from the RCSB Protein Data Bank  
 14 ([www.rcsb.org](http://www.rcsb.org)).

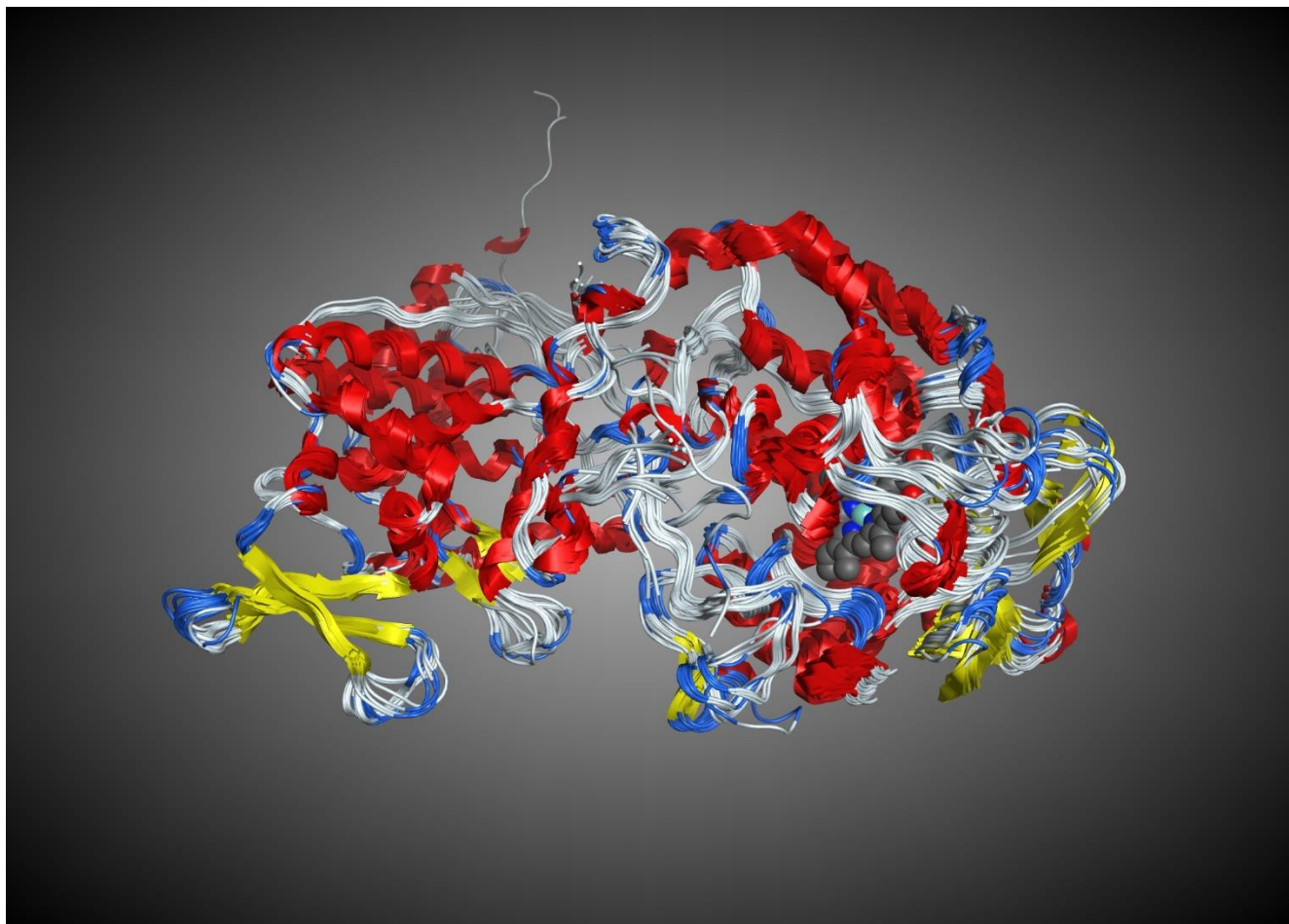
	Channel 1				Channel 2				Channel 3				
	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	D1 (Å)	D2 (Å)	Area (Å <sup>2</sup> )	% $\Delta$	File Name
<b>WT</b>	5.97	12.35	57.91	0.00	3.81	5.93	17.74	0.00	3.72	5.12	14.96	0.00	
<b>S315T</b>	4.81	11.94	45.11	-22.11	4.32	5.70	19.34	+8.99	4.05	5.15	16.38	+9.51	
<b>Novel mutations reported by Torres et al. [4]</b>													
<b>Y64S</b>	6.38	11.39	57.07	-1.44	3.52	5.52	15.26	-14.00	3.90	8.12	24.87	+66.27	Y64S.pdb
<b>Y95C</b>	6.47	11.04	56.10	-3.12	3.39	5.29	14.08	-20.63	3.48	6.99	19.10	+27.72	Y95C.pdb
<b>P131T</b>	6.34	11.46	57.06	-1.46	3.57	5.40	15.14	-14.67	3.89	8.10	24.75	+65.43	P131T.pdb
<b>A139P</b>	8.12	11.42	72.83	+25.77	3.34	5.34	14.01	-21.06	3.43	7.05	18.99	+26.96	A139P.pdb
<b>D142G</b>	6.74	11.19	59.24	+2.29	3.43	5.39	14.52	-18.17	3.73	7.50	21.97	+46.88	D142G.pdb
<b>A162V</b>	5.94	11.55	53.88	-6.95	3.38	5.99	15.90	-10.39	3.79	7.78	23.16	+54.81	A162V.pdb
<b>G269D</b>	6.64	11.52	60.08	+3.75	3.40	5.72	15.27	-13.92	3.70	7.69	22.35	+49.39	G269D.pdb
<b>T306P</b>	6.36	11.50	57.44	-0.80	3.47	5.48	14.93	-15.84	3.86	7.85	23.80	+59.09	T306P.pdb
<b>R385W</b>	6.46	11.62	58.96	+1.81	3.41	5.46	14.62	-17.59	3.74	7.79	22.88	+52.97	R385W.pdb
<b>D387G</b>	6.46	11.12	56.42	-2.57	3.40	5.32	14.21	-19.94	3.69	7.83	22.69	+51.70	D387G.pdb
<b>T394M</b>	6.33	11.54	57.37	-0.92	3.52	5.75	15.90	-10.42	3.94	7.89	24.42	+63.22	T394M.pdb
<b>Q439P</b>	7.31	11.69	67.12	+15.90	3.67	5.55	16.00	-9.85	3.97	8.29	25.85	+72.80	Q439P.pdb
<b>F483L</b>	6.33	11.20	55.68	-3.84	3.37	5.31	14.05	-20.80	3.56	7.53	21.05	+40.74	F483L.pdb
<b>A541D</b>	6.60	11.17	57.90	-0.01	3.41	5.35	14.33	-19.25	3.89	7.69	23.49	+57.06	A541D.pdb
<b>Control Mutations</b>													
<b>A110V</b>	6.77	12.47	66.30	+14.50	3.82	5.73	17.19	-3.12	3.74	6.12	17.98	+20.17	A110V.pdb
<b>L499M</b>	6.77	12.49	66.41	+14.69	3.88	5.72	17.43	-1.77	3.70	6.16	17.90	+19.67	L499M.pdb
<b>L587P</b>	6.55	12.38	63.69	+9.98	3.96	5.71	17.76	+0.08	3.62	6.35	18.05	20.69	L587P.pdb
<b>R463L</b>	6.75	12.37	65.58	+13.25	3.86	5.73	17.37	-2.10	3.75	6.67	19.64	+31.32	R463L.pdb
<b>S316G</b>	6.72	12.30	64.92	+12.11	3.84	5.61	16.92	-4.65	3.77	6.79	20.10	+34.40	S316G.pdb

16 **Supplemental Table ST3:** Functions used in estimation of MIC values

Statistical	Polynomial	Rational	Exponential
$f(x) = stdev(x)$	$f(x) = x$	$f(x, y, z) = \frac{x}{y + z}$	$f(x) = x^2$
$f(x, y, z) = max(x, y, z)$	$f(x, y) = x + y$	$f(x, y, z) = \frac{x + y}{z}$	$f(x) = \sqrt{x}$
$f(x, y, z) = min(x, y, z)$	$f(x, y) = x - y$	$f(x, y) = \frac{x}{y}$	$f(x) = x^3$
	$f(x, y, z) = x + y + z$	$f(x, y, z) = \frac{x}{y \times z}$	$f(x) = \sqrt[3]{x}$
	$f(x, y, z) = x + y - z$	$f(x, y, z) = \frac{x^2}{y \times z}$	
	$f(x, y, z) = x - y - z$		

17 **Note:**  $x, y$  and  $z$  could be any of  $A_s, \% \Delta A_s, A_h, \% \Delta A_h,$  and  $A_{min}$  values for any of the Channels 1, 2, and 3.  
 18 For instance  $f(x, y, z) = \frac{x+y}{z}$ , represent all variations of the five measurements from the three channels  
 19 such as  $f(A_s^1, A_s^2, A_s^3) = \frac{A_s^1 + A_s^2}{A_s^3}, f(A_s^1, A_s^2, A_s^3) = \frac{A_s^3 + A_s^2}{A_s^1}, f(\% \Delta A_s^1, \% \Delta A_s^2, \% \Delta A_s^3) = \frac{\% \Delta A_s^1 + \% \Delta A_s^3}{\% \Delta A_s^2}$ , etc.,  
 20 where  $A_s^1$ , for instance, is the cross-sectional area of Channel 1 measurement at the surface of the protein  
 21 structure.

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25 **Supplementary Figure SF1.** Structural superposition of the 48 x-ray crystal structures of KatG from six species  
26 illustrating the similar secondary and tertiary structures, overall 0.91 Å *RMSD*. The heme from 2CCA.pdb is  
27 shown in blue and grey.

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