

**Supplementary Table S1A.** List of EC numbers present in Table 3

1.2.1.3	Aldehyde dehydrogenase (NAD(+))
2.3.1.9	Acetyl-CoA C-acetyltransferase
2.6.1.1	Aspartate transaminase
4.2.1.17	Enoyl-CoA hydratase

Supplementary Table S1B. List of KEGG identifiers present in Table 3

hsa00010	Glycolysis / Gluconeogenesis
hsa00053	Ascorbate and aldarate metabolism
hsa00062	Fatty acid elongation
hsa00071	Fatty acid degradation
hsa00072	Synthesis and degradation of ketone bodies
hsa00220	Arginine biosynthesis
hsa00250	Alanine, aspartate and glutamate metabolism
hsa00260	Glycine, serine and threonine metabolism
hsa00270	Cysteine and methionine metabolism
hsa00280	Valine, leucine and isoleucine degradation
hsa00310	Lysine degradation
hsa00330	Arginine and proline metabolism
hsa00340	Histidine metabolism
hsa00350	Tyrosine metabolism
hsa00360	Phenylalanine metabolism
hsa00380	Tryptophan metabolism
hsa00400	Phenylalanine, tyrosine and tryptophan biosynthesis
hsa00410	beta-Alanine metabolism
hsa00561	Glycerolipid metabolism
hsa00620	Pyruvate metabolism
hsa00630	Glyoxylate and dicarboxylate metabolism
hsa00640	Propanoate metabolism
hsa00650	Butanoate metabolism
hsa00900	Terpenoid backbone biosynthesis
hsa01100	Metabolic pathways
hsa01200	Carbon metabolism
hsa01210	2-Oxocarboxylic acid metabolism
hsa01212	Fatty acid metabolism
hsa01230	Biosynthesis of amino acids



Supplementary Table S2: Variants in ALDH7A1

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
3	-	R3L	rs759866910	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-	-	-	-	-	Target peptide
3	-	R3H	rs759866910	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-	-	-	-	-	Target peptide
3	-	R3P	rs759866910	not provided ClinVar	-	-	-	-	-	Target peptide
3	-	R3C	rs796052265	not provided ClinVar	-	-	-	-	-	Target peptide
5	-	P5L		Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
5	-	P5S	rs745921838	not provided ClinVar	-	-	-	-	-	Target peptide
6	-	R6C	rs781779462	Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
7	-	A7V	rs1561674305	Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
8	-	L8P	rs796052255	not specified ClinVar	-	-	-	-	-	Target peptide
11	-	H11E	rs796052269	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar	-	-	-	-	-	Target peptide
12	-	A12D		DOI:8618 / oral cavity cancer Biomuta	-	-	-	-	-	Target peptide
18	-	L18P		Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
19	-	S19F	rs566243475	Pyridoxine-dependent epilepsy ClinVar; Seizures ClinVar; not provided ClinVar	-	-	-	-	-	Target peptide
22	-	W22C		Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
23	-	S23G	rs796052266	not provided ClinVar	-	-	-	-	-	Target peptide
25	-	P25S	rs762624752	not provided ClinVar	-	-	-	-	-	Target peptide
27	-	A27P	rs1060502950	Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
29	-	M29V		Pyridoxine-dependent epilepsy ClinVar	-	-	-	-	-	Target peptide
30	-	S30Y		DOID:0070003 / blastoma Biomuta; DOID:3571 / liver cancer Biomuta	-	-	-	-	-	Target peptide
31	3	T31I		DOID:263 / kidney cancer Biomuta; DOID:9256 / colorectal cancer Biomuta	0.69	0.76	yes			Target peptide
36	8	Q36H	rs779736481	not provided ClinVar	-0.31	0.28	yes			Target peptide
38	10	Q38K		DOID:1324 / lung cancer Biomuta	-0.06	0.67	yes			Target peptide
40	12	A40G	rs745385277	Pyridoxine-dependent epilepsy ClinVar	-0.63	0.49	yes			Target peptide
40	12	A40V	rs745385277	Pyridoxine-dependent epilepsy ClinVar	0.30	0.49	yes			Target peptide
47	19	L47V		DOID:363 / uterine cancer Biomuta	-0.57	0.02	no			Target peptide
47	19	L47F		Pyridoxine-dependent epilepsy ClinVar	-0.37	0.02	no			Target peptide
52	24	E52Q	rs765562932	Pyridoxine-dependent epilepsy ClinVar; Seizures ClinVar	-0.26	0.33	yes			Target peptide
64	36	E64D		Pyridoxine-dependent epilepsy ClinVar	-0.42	0.37	yes			Target peptide
67	39	T67M	rs543181020	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.45	0.27	yes			Target peptide
68	40	T68N	rs58528748	Pyridoxine-dependent epilepsy ClinVar; Intractable seizure ClinVar; not provided ClinVar	-0.87	0.03	no			Target peptide

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔAG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
69	41	Y69C	rs796052258	not provided ClinVar	-1.08	0.54	yes			
79	51	R79K	rs781361567	not provided ClinVar	-0.62	0.33	yes			
79	51	R79G	rs794727259	not provided ClinVar	-1.42	0.33	yes			
81	53	R81L		Pyridoxine-dependent epilepsy ClinVar	-0.30	0.27	yes			
82	54	Q82K		DOID:3571 / liver cancer Biomuta	-0.89	0.14	no			
83	55	A83T	rs1561672611	Pyridoxine-dependent epilepsy ClinVar	-0.81	0.06	no			
87	59	D87H		Pyridoxine-dependent epilepsy ClinVar; DOID:11934 / head and neck cancer Biomuta	-0.76	0.08	no			
88	60	Y88F	rs376294954	Pyridoxine-dependent epilepsy ClinVar	-0.72	0.02	no			
95	67	A95T	rs551163406	Pyridoxine-dependent epilepsy ClinVar	-1.47	0	no			
96	68	R96G		Pyridoxine-dependent epilepsy ClinVar	-1.17	0.37	yes			
98	70	A98S		DOID:1324 / lung cancer Biomuta	-1.15	0.06	no			
106	78	P106S		DOID:1909 / melanoma Biomuta	-0.48	0.61	yes		yes	
106	78	P106T		DOID:3571 / liver cancer Biomuta	-0.46	0.61	yes	yes	yes	
108	80	P108S		Pyridoxine-dependent epilepsy ClinVar; DOID:1909 / melanoma Biomuta	-0.47	0.3	yes	yes	yes	
109	81	K109T		DOID:1324 / lung cancer Biomuta	-0.31	0.65	yes	yes	yes	
109	81	K109Q		DOID:1324 / lung cancer Biomuta	0.19	0.65	yes	yes	yes	
110	82	R110L		DOID:10283 / prostate cancer Biomuta	0.32	0.06	no			
110	82	R110G	rs121912708	not specified ClinVar	-1.05	0.06	no			
111	83	G111E		Pyridoxine-dependent epilepsy ClinVar	-0.41	0	no			
114	86	V114A		DOID:1909 / melanoma Biomuta	-2.17	0	no			
119	91	D119N	rs1212969829	Pyridoxine-dependent epilepsy ClinVar; DOID:363 / uterine cancer Biomuta	-0.46	0.45	yes	yes	yes	
120	92	A120D		Pyridoxine-dependent epilepsy ClinVar	-1.48	0.24	yes			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
120	92	A120G	rs549279821	Pyridoxine-dependent epilepsy ClinVar	-1.35	0.24	yes			
122	94	R122P	rs796052256	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-1.26	0.38	yes	yes		
122	94	R122Q		Pyridoxine-dependent epilepsy ClinVar	-0.58	0.38	yes	yes		
122	94	R122W	rs370624118	Pyridoxine-dependent epilepsy ClinVar; DOI:3963 / thyroid carcinoma Biomuta; not specified ClinVar; not provided ClinVar; Seizures ClinVar; DOI:363 / uterine cancer Biomuta	-0.50	0.38	yes	yes		
125	97	I125V	rs117295656	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar; Seizures ClinVar; not provided ClinVar	-0.29	0.15	no			
129	101	G129V		DOI:363 / uterine cancer Biomuta	2.04	0	no			
144	116	V144M		Pyridoxine-dependent epilepsy ClinVar	0.58	0.18	no			
148	120	Q148K		DOI:3571 / liver cancer Biomuta	-0.32	0.38	yes	yes		
151	123	V151A	rs1561667040	Seizures ClinVar	-1.13	0	no			
152	124	D152H		DOI:11054 / urinary bladder cancer Biomuta	-0.16	0.36	yes	yes	yes	
154	126	C154R	rs1057520885	not provided ClinVar	-1.90	0	no			
157	129	A157S		DOI:0070003 / blastoma Biomuta	-1.05	0	no			
160	132	L160V		DOI:1324 / lung cancer Biomuta	-0.94	0.09	no			
165	137	G165E		DOI:11934 / head and neck cancer Biomuta	0.11	0.43	yes	yes		
165	137	G165V		Pyridoxine-dependent epilepsy ClinVar	0.05	0.43	yes	yes		
165	137	G165A	rs375491094	not provided ClinVar	0.02	0.43	yes	yes		
168	140	I168T		DOI:363 / uterine cancer Biomuta	-0.26	0.84	yes	yes	yes	
171	143	S171F		DOI:363 / uterine cancer Biomuta	-0.25	0.23	yes		yes	
173	145	R173T		DOI:1324 / lung cancer Biomuta	-1.06	0.28	yes		yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
177	149	A177P	rs140102105	not provided ClinVar	-0.86	0.2	no			
177	149	A177E	rs764417585	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY, PYRIDOXINE-DEPENDENT DisGeNet	-0.39	0.2	no			
178	150	L178M		DOID:3571 / liver cancer Biomuta	-0.26	0.24	yes	yes	yes	
179	151	I179T	rs763217060	not provided ClinVar	-1.19	0.2	no			
181	153	Q181R	rs796052257	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	0.37	0.45	yes	yes	yes	
185	157	V185L	rs61757685	Pyridoxine-dependent epilepsy ClinVar	0.01	0.14	no			
185	157	V185I	rs61757685	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.04	0.14	no			
190	162	I190F		DOID:1324 / lung cancer Biomuta	-1.59	0	no			
191	163	I191V	rs1060499755	Abnormality of brain morphology DisGeNet; Abnormality of brain morphology ClinVar	-0.97	0.05	no			
192	164	T192M	rs376917645	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.52	0.04	no			
193	165	A193T	rs773503933	DOID:0070003 / blastoma Biomuta; Pyridoxine-dependent epilepsy ClinVar; DOID:3571 / liver cancer Biomuta; not provided ClinVar	-0.70	0.18	no			
195	167	N195S	rs372660425	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY, PYRIDOXINE-DEPENDENT DisGeNet; not provided ClinVar	-0.71	0.04	no			Transition state stabilizer
196	168	F196L		DOID:9256 / colorectal cancer Biomuta	-2.07	0.12	no			
197	169	P197L		DOID:1909 / melanoma Biomuta	-0.47	0	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔAG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
197	169	P197S	rs779652673	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet; not provided ClinVar	-1.21	0	no			
199	171	A199V	rs121912709	Pyridoxine-dependent epilepsy ClinVar; Pyridoxine-dependent epilepsy (PDE) HUMSAVAR; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet	-0.28	0	no			
200	172	V200A		DOID:363 / uterine cancer Biomuta	-1.71	0.06	no			
202	174	G202V		DOID:2531 / hematologic cancer Biomuta; Pyridoxine-dependent epilepsy (PDE) HUMSAVAR	1.92	0	no			
203	175	W203G	rs55896752	not provided ClinVar	-3.13	0.06	no			
208	180	A208V	rs200433565	Seizures ClinVar	-1.38	0	no			
211	183	C211F	rs1131691976	not provided ClinVar	-1.76	0	no			
216	188	L216P		Pyridoxine-dependent epilepsy ClinVar	-3.14	0	no			
219	191	G219R		DOID:3963 / thyroid carcinoma Biomuta	-0.65	0.02	no			
219	191	G219A		Pyridoxine-dependent epilepsy ClinVar	-0.01	0.02	no			
219	191	G219E		DOID:1324 / lung cancer Biomuta	-1.08	0.02	no			
222	194	T222A	rs777829351	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.47	0.4	yes			
223	195	T223N		DOID:3571 / liver cancer Biomuta	-1.08	0	no			
224	196	S224F		Pyridoxine-dependent epilepsy ClinVar	0.05	0.02	no			
225	197	L225F		DOID:9256 / colorectal cancer Biomuta	-0.90	0	no			
228	200	V228M	rs201832111	Pyridoxine-dependent epilepsy ClinVar	-0.24	0	no			
228	200	V228A		Pyridoxine-dependent epilepsy ClinVar	-0.54	0	no			
229	201	A229V	rs1473102872	Pyridoxine-dependent epilepsy ClinVar	0.06	0	no			
237	209	V237F		DOID:1909 / melanoma Biomuta	-1.10	0.08	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔAG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
260	232	A260T		DOID:10283 / prostate cancer Biomuta	-0.82	0.25	yes			
261	233	M261V		Pyridoxine-dependent epilepsy ClinVar	-0.93	0	no			
262	234	A262T		DOID:363 / uterine cancer Biomuta	-0.48	0	no			
263	235	K263R		Pyridoxine-dependent epilepsy ClinVar	0.13	0.6	yes			
266	238	R266Q	rs796052259	not provided ClinVar	-1.15	0.25	yes			
272	244	F272L		DOID:9256 / colorectal cancer Biomuta	-2.09	0.08	no			
276	248	T276P	rs796052260	not provided ClinVar	-1.11	0.2	no			Nucleotide binding
278	250	V278L		Pyridoxine-dependent epilepsy ClinVar	-0.85	0.52	yes		yes	Nucleotide binding
281	253	Q281H		Pyridoxine-dependent epilepsy ClinVar	0.13	0.46	yes		yes	
281	253	Q281K		DOID:3571 / liver cancer Biomuta	-0.05	0.46	yes		yes	
285	257	M285V		Pyridoxine-dependent epilepsy ClinVar	-0.83	0.24	yes		yes	
287	259	Q287R	rs796052261	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.04	0.61	yes	yes	yes	
289	261	R289W		DOID:3571 / liver cancer Biomuta	-1.03	0.12	no			
291	263	G291W		Pyridoxine-dependent epilepsy ClinVar	-0.42	0.27	yes			
291	263	G291E		Pyridoxine-dependent epilepsy (PDE) HUMSAVAR	-0.61	0.27	yes			
296	268	E296K		DOID:1909 / melanoma Biomuta	-0.68	0.04	no			Proton acceptor
298	270	G298R		DOID:363 / uterine cancer Biomuta	-0.61	0.01	no			
300	272	N300D		Pyridoxine-dependent epilepsy ClinVar	-0.59	0.03	no			
301	273	N301I	rs121912711	Pyridoxine-dependent epilepsy ClinVar; Pyridoxine-dependent epilepsy (PDE) HUMSAVAR; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet	-0.02	0.01	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
303	275	I303V		DOID:1324 / lung cancer Biomuta; Pyridoxine-dependent epilepsy ClinVar	0.07	0.01	no			
305	277	A305S		DOID:1324 / lung cancer Biomuta; DOID:1909 / melanoma Biomuta	-0.80	0	no			
305	277	A305G	rs141775154	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-1.66	0	no			
312	284	S312R	rs1561654302	Pyridoxine-dependent epilepsy ClinVar	0.36	0.54	yes	yes		
316	288	P316S		DOID:1909 / melanoma Biomuta	-0.29	0.54	yes	yes		
318	290	A318T	rs936151635	Pyridoxine-dependent epilepsy ClinVar	-0.87	0.02	no			
318	290	A318P	rs936151635	Pyridoxine-dependent epilepsy ClinVar	-2.04	0.02	no			
319	291	L319H	rs1057522342	not provided ClinVar	-1.59	0.21	yes	yes	yes	
321	293	A321T	rs746212816	DOID:3070 / malignant glioma Biomuta; not provided ClinVar	-1.09	0.01	no			
327	299	G327S	rs1554099008	not provided ClinVar	-0.85	0	no			
329	301	R329G		DOID:3963 / thyroid carcinoma Biomuta	-1.89	0.1	no			
329	301	R329K	rs864622558	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet	-1.25	0.1	no			
329	301	R329S	rs761295869	Pyridoxine-dependent epilepsy ClinVar	-1.23	0.1	no			
332	304	T332I	rs543182575	Pyridoxine-dependent epilepsy ClinVar	-0.89	0.01	no			
332	304	T332S	rs543182575	Pyridoxine-dependent epilepsy ClinVar; Seizures ClinVar	-0.06	0.01	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔAG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
333	305	A333V	rs144625212	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar	0.09	0.03	no			
335	307	R335Q	rs754449549	Pyridoxine-dependent epilepsy ClinVar; Pyridoxine-dependent epilepsy (PDE) HUMSAVAR; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet; not provided ClinVar	-1.12	0.01	no			
337	309	F337C	rs747834606	Pyridoxine-dependent epilepsy ClinVar	-2.35	0	no			
338	310	I338L		DOID:2531 / hematologic cancer Biomuta	-0.71	0	no			
339	311	H339R	rs199767457	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.78	0.16	no			
341	313	S341N	rs141701364	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar	-0.46	0.47	yes			
346	318	V346A		DOID:1909 / melanoma Biomuta	-2.06	0	no			
349	321	R349T	rs553114356	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.83	0.4	yes			
355	327	A355T		DOID:9256 / colorectal cancer Biomuta	-0.49	0.58	yes			
356	328	Q356E	rs138675705	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.04	0.78	yes			
356	328	Q356R		DOID:1909 / melanoma Biomuta	0.13	0.78	yes			
357	329	I357V	rs761011399	not specified ClinVar	-0.31	0.11	no			
358	330	R358L	rs144671885	Pyridoxine-dependent epilepsy ClinVar; Seizures ClinVar	0.18	0.45	yes	yes		
358	330	R358Q		DOID:1793 / pancreatic cancer Biomuta	-0.58	0.45	yes	yes		
362	334	P362S	rs532800318	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-1.10	0	no			
363	335	W363R	rs886044173	not provided ClinVar	-0.96	0.19	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
364	336	D364N		DOID:10283 / prostate cancer Biomuta	-0.30	0.4	yes			
365	337	P365H		DOID:3571 / liver cancer Biomuta	-0.37	0.85	yes			
365	337	P365S	rs370869432	Pyridoxine-dependent epilepsy ClinVar; DOID:9256 / colorectal cancer Biomuta; not provided ClinVar	-0.46	0.85	yes			
366	338	N366K		Pyridoxine-dependent epilepsy ClinVar	-0.12	0.63	yes			
375	347	K375R		Pyridoxine-dependent epilepsy ClinVar	-0.56	0.28	yes		yes	
376	348	Q376K	rs564187364	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.41	0.32	yes			
377	349	A377T		Pyridoxine-dependent epilepsy ClinVar	-0.80	0.16	no			
378	350	V378L		DOID:1793 / pancreatic cancer Biomuta	-0.34	0.13	no			
380	352	M380I		DOID:3571 / liver cancer Biomuta	0.03	0.68	yes			
384	356	A384E		DOID:3571 / liver cancer Biomuta	-1.55	0.05	no			
384	356	A384T	rs140947675	Pyridoxine-dependent epilepsy ClinVar; Leukoencephalopathy ClinVar; not provided ClinVar	-0.78	0.05	no			
386	358	E386K		DOID:3371 / chondrosarcoma Biomuta	-0.91	0.2	no			
388	360	A388G	rs1561651205	Pyridoxine-dependent epilepsy ClinVar	-1.54	0	no			
394	366	T394I		DOID:1324 / lung cancer Biomuta	-0.25	0.58	yes			
395	367	V395G		Pyridoxine-dependent epilepsy (PDE) HUMSAVAR	-3.27	0.26	yes			
398	370	G398V	rs864622557	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet	-1.06	0.18	no			
399	371	G399V		Pyridoxine-dependent epilepsy ClinVar	-0.83	0.13	no			
403	375	D403N	rs796052262	not provided ClinVar	0.04	1	yes			
404	376	R404C		DOID:1909 / melanoma Biomuta	-0.59	0.41	yes			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
404	376	R404H		DOID:10534 / stomach cancer Biomuta; DOID:9256 / colorectal cancer Biomuta; DOID:1909 / melanoma Biomuta	-0.51	0.41	yes			
409	381	V409L	rs796052263	not provided ClinVar	-0.95	0	no			
411	383	P411L	rs780233639	Seizures ClinVar; not provided ClinVar	-0.62	0.04	no			
411	383	P411Q		DOID:0070003 / blastoma Biomuta; DOID:3571 / liver cancer Biomuta	-0.78	0.04	no			
412	384	T412I		Pyridoxine-dependent epilepsy ClinVar; DOID:3963 / thyroid carcinoma Biomuta	-0.54	0	no			
412	384	T412A	rs2306618	not specified ClinVar; Pyridoxine-dependent epilepsy ClinVar; Polymorphism HUMSAVAR; DOID:9256 / colorectal cancer Biomuta; Seizures ClinVar	-1.12	0	no			
414	386	V414M		DOID:1324 / lung cancer Biomuta; Pyridoxine-dependent epilepsy ClinVar	-1.14	0	no			
415	387	T415K		DOID:3070 / malignant glioma Biomuta	-1.19	0.14	no			
415	387	T415I		Pyridoxine-dependent epilepsy ClinVar	-0.17	0.14	no			
418	390	G418D		DOID:263 / kidney cancer Biomuta	0.33	0.48	yes			
421	393	A421V	rs753598402	not provided ClinVar	-0.78	0.15	no			
423	395	I423V	rs760266177	not provided ClinVar	-0.43	0.08	no			
424	396	A424T		Pyridoxine-dependent epilepsy ClinVar	-0.81	0	no			
426	398	T426A	rs150305320	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.81	0.49	yes			
427	399	E427G		DOID:4362 / cervical cancer Biomuta	-0.76	0.24	yes			
427	399	E427D	rs796052271	not provided ClinVar	-0.69	0.24	yes			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
427	399	E427Q	rs121912707	Pyridoxine-dependent epilepsy ClinVar; Pyridoxine-dependent epilepsy (PDE) HUMSAVAR; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet; not provided ClinVar; Seizures DisGeNet; Epilepsy DisGeNet; Seizures ClinVar	-0.55	0.24	yes			
430	402	A430S		DOID:1612 / breast cancer Biomuta	-0.49	0.01	no			
430	402	A430V		DOID:1612 / breast cancer Biomuta	-0.46	0.01	no			
431	403	P431A		DOID:1793 / pancreatic cancer Biomuta	-0.96	0.02	no			
433	405	L433P		DOID:9256 / colorectal cancer Biomuta	-3.50	0.01	no			
434	406	Y434S	rs747597620	not provided ClinVar	-1.80	0.02	no			
434	406	Y434C	rs747597620	DOID:2994 / germ cell cancer Biomuta; Pyridoxine-dependent epilepsy ClinVar; DOID:2394 / ovarian cancer Biomuta; not provided ClinVar	-0.86	0.02	no			
439	411	K439Q	rs12514417	not specified ClinVar; Pyridoxine-dependent epilepsy ClinVar; Polymorphism HUMSAVAR; DOID:9256 / colorectal cancer Biomuta; Seizures ClinVar	-1.05	0.21	yes			
441	413	E441K		DOID:11054 / urinary bladder cancer Biomuta	-0.97	0.18	no			
446	418	A446V		DOID:2394 / ovarian cancer Biomuta	-0.88	0.49	yes			
452	424	K452N	rs756859037	Pyridoxine-dependent epilepsy ClinVar	-0.72	0.32	yes			
458	430	S458N		Pyridoxine-dependent epilepsy (PDE) HUMSAVAR	-0.70	0	no			
459	431	I459F	rs186558364	not provided ClinVar	-1.82	0	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔAG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
459	431	I459T	rs1057518529	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar	-2.99	0	no			
459	431	I459M		DOID:1324 / lung cancer Biomuta	-1.66	0	no			
463	435	D463Y		DOID:363 / uterine cancer Biomuta	-0.17	0.41	yes			
465	437	G465D		DOID:363 / uterine cancer Biomuta	0.08	0.33	yes	yes	yes	
469	441	R469C		DOID:3070 / malignant glioma Biomuta	-0.50	0.43	yes			
469	441	R469H	rs147940248	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	-0.62	0.43	yes			
471	443	L471P		DOID:9256 / colorectal cancer Biomuta	-2.33	0.64	yes	yes	yes	
471	443	L471F		Pyridoxine-dependent epilepsy ClinVar; DOID:10534 / stomach cancer Biomuta	-0.60	0.64	yes	yes	yes	
474	446	K474E		DOID:10283 / prostate cancer Biomuta	0.05	0.86	yes	yes	yes	
477	449	D477E		DOID:3571 / liver cancer Biomuta	-0.35	0.3	yes	yes	yes	
480	452	I480T	rs886059849	Pyridoxine-dependent epilepsy ClinVar	-0.99	0.12	no			
481	453	V481L	rs796052264	not provided ClinVar	-1.20	0.3	yes	yes	yes	
481	453	V481E	rs144701796	not provided ClinVar	-1.84	0.3	yes	yes	yes	
484	456	N484S	rs1561648688	Pyridoxine-dependent epilepsy ClinVar	-0.05	0.3	yes	yes	yes	
487	459	T487A		DOID:2531 / hematologic cancer Biomuta	-1.14	0.01	no			
494	466	G494V	rs763418390	Pyridoxine-dependent epilepsy ClinVar; not provided ClinVar	0.79	0.44	yes	yes	yes	
505	477	G505R	rs556400964	Pyridoxine-dependent epilepsy ClinVar; EPILEPSY. PYRIDOXINE-DEPENDENT DisGeNet; not provided ClinVar	-0.65	0.05	no			
507	479	E507A	rs80049945	Pyridoxine-dependent epilepsy ClinVar	-0.76	0	no			
511	483	D511G		Pyridoxine-dependent epilepsy ClinVar	-0.94	0.45	yes	yes	yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
516	488	Y516H		DOID:0070003 / blastoma Biomuta; DOID:3571 / liver cancer Biomuta	-1.28	0	no			
516	488	Y516C		Pyridoxine-dependent epilepsy ClinVar	-2.04	0	no			
517	489	M517I	rs1064794774	not provided ClinVar	-1.01	0.02	no			
519	491	R519M		DOID:363 / uterine cancer Biomuta	-0.21	0.54	yes	yes	yes	
519	491	R519K	rs561343926	Pyridoxine-dependent epilepsy ClinVar	-0.47	0.54	yes	yes	yes	
520	492	S520F	rs1554097854	Pyridoxine-dependent epilepsy ClinVar; DOID:9256 / colorectal cancer Biomuta	-0.07	0.24	yes	yes	yes	
522	494	C522S	rs1057521316	not provided ClinVar	-0.92	0.24	yes	yes	yes	
523	495	T523N		DOID:363 / uterine cancer Biomuta	-0.34	0.45	yes	yes	yes	
523	495	T523A	rs61757684	Pyridoxine-dependent epilepsy ClinVar; not specified ClinVar; Seizures ClinVar; not provided ClinVar	-0.26	0.45	yes	yes	yes	
524	496	I524V		DOID:263 / kidney cancer Biomuta	-0.39	0.36	yes	yes	yes	
530	502	L530F		DOID:0070003 / blastoma Biomuta; DOID:3571 / liver cancer Biomuta	-0.03	0.87	yes	yes	yes	

Variants in ALDH7A1 are derived from different sources including Humsavar, OMIM, ClinVar, Biomuta,. Variants are mapped on the PDB file 4ZUL, chain A. $\Delta\Delta G$ values are predicted with INPS starting from structure. RSA= Relative Solvent Accessibility computed with DSSP. Surface residues are those with RSA ≥ 0.2 . Residues that are part of the tetrameric interface are computed from the Biological Assembly of 4ZUL. Residues in non-tetrameric interfaces are predicted with ISPRED4. Sites and regions are derived from UniProt annotations. In red we highlighted the mutation reported in [33].

Supplementary Table S3: Variants in ACATI

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
1	-	M1K	rs120074142	Deficiency of acetyl-CoA acetyltransferase ClinVar						Target peptide
1	-	M1T	rs120074142	Deficiency of acetyl-CoA acetyltransferase ClinVar						Target peptide
1	-	M1V	rs1305448140	Deficiency of acetyl-CoA acetyltransferase ClinVar						Target peptide
5	-	A5P	rs3741056	Deficiency of acetyl-CoA acetyltransferase ClinVar; Polymorphism HUMSAVAR; not specified ClinVar; DOI:9256 / colorectal cancer Biomuta						Target peptide
10	-	S10N	rs886047595	Deficiency of acetyl-CoA acetyltransferase ClinVar						Target peptide
13	-	R13G		DOI:3571 / liver cancer Biomuta						Target peptide
27	-	R27I		DOI:363 / uterine cancer Biomuta						Target peptide
29	-	V29L	rs764142914	DOI:10283 / prostate cancer Biomuta; DOI:1793 / pancreatic cancer Biomuta; not provided ClinVar						Target peptide
31	31	R31W	rs199952982	not provided ClinVar						Target peptide
35	35	S35L		DOI:1612 / breast cancer Biomuta						
36	36	K36Q		DOI:1324 / lung cancer Biomuta						
45	45	V45L		DOI:363 / uterine cancer Biomuta	-1.17	0.06	no			
52	52	I52T		Deficiency of acetyl-CoA acetyltransferase ClinVar	-2.47	0	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
55	55	F55C		DOID:363 / uterine cancer Biomuta	-1.95	0.39	yes	yes	yes	
57	57	G57C		DOID:1324 / lung cancer Biomuta	0.01	0.19	no			
66	66	K66N		DOID:3571 / liver cancer Biomuta	-0.53	0.5	yes		yes	
68	68	G68V	rs794727475	not provided ClinVar	0.26	0	no			
73	73	Q73P	rs779758622	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.93	0.46	yes		yes	
75	75	A75V		DOID:363 / uterine cancer Biomuta	-1.03	0	no			
81	81	I81N		DOID:10283 / prostate cancer Biomuta	-3.19	0.09	no			
89	89	A89V		DOID:3371 / chondrosarcoma Biomuta	1.73	0	no			
90	90	Y90C		DOID:9256 / colorectal cancer Biomuta	-1.26	0.16	no	yes		
92	92	G92S	rs1591362402	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.72	0	no			
93	93	N93S	rs120074145	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; Ketoacidosis DisGeNet	-0.49	0	no			
98	98	G98V		DOID:2394 / ovarian cancer Biomuta	-0.86	0.95	yes	yes	yes	
99	99	E99D		DOID:1324 / lung cancer Biomuta	-0.74	0.18	no			
100	100	G100E	rs1591362472	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.82	0.56	yes	yes	yes	
101	101	Q101K	rs1591362483	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.16	0.92	yes	yes	yes	
103	103	P103H		DOID:1909 / melanoma Biomuta	-1.07	0.07	no			
116	116	S116Y		DOID:363 / uterine cancer Biomuta	-0.02	0.72	yes	yes	no	
117	117	T117P		DOID:363 / uterine cancer Biomuta	-1.11	0.01	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
118	118	P118A		DOID:1324 / lung cancer Biomuta; DOID:11054 / urinary bladder cancer Biomuta; DOID:10534 / stomach cancer Biomuta	-0.99	0.46	yes	yes	yes	
124	124	K124R	rs1037467160	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.15	0.2	yes	yes	yes	
124	124	K124E	rs1591363715	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.03	0.2	yes	yes	yes	
126	126	C126S	rs1278227329	Deficiency of acetyl-CoA acetyltransferase ClinVar	-					Active site
127	127	A127V	rs1591363760	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.27	0.03	no			
129	129	G129E		DOID:11054 / urinary bladder cancer Biomuta	-1.14	0	no			
130	130	M130I		DOID:2994 / germ cell cancer Biomuta; DOID:2394 / ovarian cancer Biomuta	-0.96	0	no			
132	132	A132G	rs1591363786	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.64	0	no			
134	134	M134I		DOID:1324 / lung cancer Biomuta	-0.49	0.01	no			
135	135	M135V		DOID:9256 / colorectal cancer Biomuta	-0.77	0.35	yes	yes	no	
139	139	S139N		DOID:2994 / germ cell cancer Biomuta;						
141	141	M141L	rs750876321	DOID:2394 / ovarian cancer Biomuta not provided ClinVar	-0.79	0.11	no	yes	yes	
143	143	G143V		DOID:3571 / liver cancer Biomuta	-1.43	0.44	yes	yes	yes	
144	144	H144P	rs1025180934	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.77	0.72	yes	yes	yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
145	145	Q145E	rs120074148	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; Ketoacidosis DisGeNet	-0.81	0.25	yes	yes	no	
146	146	D146N		DOI:11054 / urinary bladder cancer Biomuta	-0.70	0.26	yes		no	
147	147	V147L		DOI:1324 / lung cancer Biomuta	-0.88	0	no			
152	152	G152A	rs762991875	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; not provided ClinVar; Ketoacidosis DisGeNet; Neurologic Deficits DisGeNet	-0.88	0	no			
154	154	E154K	rs1198149157	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.45	0	no			
156	156	M156I		DOI:3571 / liver cancer Biomuta	-1.45	0.01	no			
158	158	N158S	rs199524907	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; Ketoacidosis DisGeNet; not provided ClinVar	-0.02	0.55	yes		yes	
158	158	N158D	rs148639841	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR;	-0.25	0.55	yes		yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
171	171	G171C		DOID:1324 / lung cancer Biomuta	0.13	0.96	yes	yes	yes	
176	176	E176K		DOID:1612 / breast cancer Biomuta	-0.37	0.29	yes		yes	
176	176	E176Q		DOID:4362 / cervical cancer Biomuta	-0.33	0.29	yes		yes	
178	178	L178F	rs1320114846	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.17	0.09	no	yes		
183	183	G183R	rs120074141	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR;	-0.04	0.08	no	yes		
186	186	D186G		DOID:10534 / stomach cancer Biomuta	-0.68	0.02	no	yes		
186	186	D186Y	rs1591367592	Deficiency of acetyl-CoA acetyltransferase ClinVar	0.65	0.02	no	yes		
192	192	H192R		Episodic metabolic acidosis ClinVar; Abnormality of acetylcarnitine metabolism ClinVar	-0.73	0.29	yes	yes	yes	
192	192	H192N		DOID:363 / uterine cancer Biomuta	-0.98	0.29	yes	yes	yes	
193	193	M193R	rs541517496	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.32	0.09	no			
193	193	M193T	rs541517496	Deficiency of acetyl-CoA acetyltransferase ClinVar	-2.33	0.09	no			
201	201	A201V	rs1591368724	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.74	0.05	no			
203	203	K203R		DOID:1115 / sarcoma Biomuta	0.02	0.58	yes		yes	
208	208	R208G	rs532190594	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.62	0.21	yes		yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
208	208	R208Q	rs370720208	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; DOI:3963 / thyroid carcinoma Biomuta; DOI:9256 / colorectal cancer Biomuta; not provided ClinVar; DOI:363 / uterine cancer Biomuta; Ketoacidosis DisGeNet	-1.36	0.21	yes		yes	
211	211	Q211R		DOI:0070003 / blastoma Biomuta; DOI:3571 / liver cancer Biomuta	-0.58	0	no			
215	215	A215N	rs1591368794	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.81	0	no			
215	215	A215V		DOI:3070 / malignant glioma Biomuta	-0.89	0	no			
218	218	S218F	rs879255505	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; Ketoacidosis DisGeNet	-0.69	0	no			
218	218	S218A		DOI:1612 / breast cancer Biomuta	-0.89	0	no			
219	219	Y219H	rs1437567292	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.30	0.05	no			Binding site
222	222	S222R	rs1591368826	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.23	0	no			
225	225	A225E	rs1385465985	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.32	0.02	no			
239	239	T239A		DOI:363 / uterine cancer Biomuta	0.00	0.49	yes			no
240	240	V240D		DOI:1324 / lung cancer Biomuta	-2.14	0.1	no			
241	241	T241A		Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.24	0.7	yes			yes
247	247	D247E		DOI:2531 / hematologic cancer Biomuta	0.11	0.6	yes			yes

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
252	252	E252K		Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.21	0.29	yes		no	
253	253	D253N	rs869312946	Inborn genetic diseases ClinVar	-0.56	0	no			
253	253	D253E	rs983216159	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.18	0	no			
254	254	E254K	rs1591370241	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.92	0.19	no			
255	255	E255D	rs794727893	Deficiency of acetyl-CoA acetyltransferase ClinVar; not provided ClinVar	-0.71	0.07	no			
255	255	E255A	rs1591370252	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.48	0.07	no			
256	256	Y256S		DOI:0070003 / blastoma Biomuta;						
256	256	Y256N	rs794727894	DOI:3571 / liver cancer Biomuta not provided ClinVar	-2.23	0.08	no			
257	257	K257T	rs370652435	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.47	0.54	yes		no	
258	258	R258C	rs753816946	Deficiency of acetyl-CoA acetyltransferase ClinVar; DOI:1909 / melanoma Biomuta	-0.44	0.52	yes		yes	
260	260	D260N		DOI:363 / uterine cancer Biomuta	-0.12	0.53	yes		yes	
262	262	S262I		DOI:3571 / liver cancer Biomuta	0.89	0.55	yes		yes	
262	262	S262N		DOI:363 / uterine cancer Biomuta	-0.03	0.55	yes		yes	
276	276	G276V		DOI:3571 / liver cancer Biomuta	0.25	0.14	no			
277	277	T277A		DOI:363 / uterine cancer Biomuta	-1.20	0.12	no			
277	277	T277P	rs1591371019	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.43	0.12	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
282	282	N282S		DOI:0070003 / blastoma Biomuta; DOI:1793 / pancreatic cancer Biomuta	-0.65	0	no			
282	282	N282H	rs750195919	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.28	0	no			
283	283	A283V		DOI:263 / kidney cancer Biomuta	-0.44	0.05	no			
283	283	A283D		DOI:363 / uterine cancer Biomuta	-1.98	0.05	no			
284	284	S284N	rs1591371045	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.78	0.19	no			Binding site
285	285	T285I	rs1239221388	Deficiency of acetyl-CoA acetyltransferase ClinVar	0.30	0.2	yes		yes	
287	287	N287K	rs1351732995	not provided ClinVar	-0.52	0	no			
296	296	M296V		DOI:363 / uterine cancer Biomuta	-0.97	0	no			
297	297	T297M	rs886041122	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; Intellectual disability ClinVar; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; Epilepsy ClinVar; not provided ClinVar; Ketoacidosis DisGeNet	-0.98	0.04	no			
297	297	T297K	rs886041122	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; Ketoacidosis DisGeNet	-0.79	0.04	no			
301	301	A301V		DOI:10534 / stomach cancer Biomuta	-0.84	0.04	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
301	301	A301P	rs1420321267	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD)	-2.06	0.04	no			
302	302	K302N		[MIM:203750] HUMSAVAR DOI:1612 / breast cancer Biomuta	-0.66	0.74	yes		no	
312	312	I312T	rs120074146	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD)	-3.06	0.09	no			
317	317	D317E		[MIM:203750] HUMSAVAR; Ketoacidosis DisGeNet DOI:3963 / thyroid carcinoma Biomuta	-0.11	0.29	yes	yes	no	
317	317	D317N	rs780486838	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.40	0.29	yes	yes	no	
318	318	A318T		DOI:1793 / pancreatic cancer Biomuta;	-0.42	0.13	no	yes		
318	318	A318S		DOI:363 / uterine cancer Biomuta DOI:3571 / liver cancer Biomuta	-0.33	0.13	no	yes		
321	321	E321D		DOI:0070003 / blastoma Biomuta; DOI:3571 / liver cancer Biomuta	0.43	0.62	yes		yes	
323	323	I323V	rs1282394804	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.25	0.16	no			
323	323	I323T	rs755806238	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.43	0.16	no			
327	327	I327V	rs150038447	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.56	0.16	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
328	328	A328V	rs1057517702	not specified ClinVar	-0.82	0	no			
333	333	A333P	rs120074147	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; Ketoacidosis DisGeNet	-1.79	0	no			
334	334	S334F		DOI:363 / uterine cancer Biomuta	-0.37	0.4	yes		yes	
335	335	M335I		DOI:3571 / liver cancer Biomuta	-0.68	0.48	yes	yes	yes	
337	337	L337R		DOI:1612 / breast cancer Biomuta	-1.93	0.08	no			
337	337	L337F		DOI:1324 / lung cancer Biomuta	-0.86	0.08	no			
341	341	G341R		DOI:1909 / melanoma Biomuta	-0.18	0.8	yes			no
347	347	I347T	rs1338023969	Deficiency of acetyl-CoA acetyltransferase ClinVar	-2.93	0	no			
350	350	W350C		DOI:3571 / liver cancer Biomuta	-2.16	0.01	no			
353	353	N353K	rs1591374629	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.47	0.01	no			
354	354	E354V	rs1591374632	Deficiency of acetyl-CoA acetyltransferase ClinVar	0.15	0	no			
355	355	A355V		DOI:1793 / pancreatic cancer Biomuta	-0.77	0.07	no			
357	357	S357C		DOI:4362 / cervical cancer Biomuta	-0.46	0	no			
357	357	S357I		DOI:3571 / liver cancer Biomuta	0.09	0	no			
362	362	A362T		DOI:10534 / stomach cancer Biomuta	-1.10	0	no			
364	364	I364T		DOI:10534 / stomach cancer Biomuta	-1.66	0.15	no			
365	365	K365R		DOI:1324 / lung cancer Biomuta	0.15	0.48	yes		yes	
369	369	I369V	rs1591374695	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.61	0.08	no			
372	372	Q372K		DOI:3963 / thyroid carcinoma Biomuta	-0.04	0.65	yes			no

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
375	375	N375S	rs373771053	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet	-0.83	0.01	no			
377	377	N377T		DOI:1612 / breast cancer Biomuta	-0.36	0.05	no			
379	379	G379V	rs120074143	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; Ketoacidosis DisGeNet	-1.32	0.01	no			
379	379	G379A		DOI:11054 / urinary bladder cancer Biomuta	-1.04	0.01	no			
380	380	A380T	rs120074140	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; 3-ketothiolase deficiency (3KTD) [MIM:203750] HUMSAVAR; Ketoacidosis DisGeNet; Neurologic Deficits DisGeNet	-0.71	0	no			
380	380	A380S		DOI:10283 / prostate cancer Biomuta	-0.47	0	no			
381	381	V381A		DOI:9256 / colorectal cancer Biomuta; DOI:1909 / melanoma Biomuta	-1.51	0	no			
382	382	S382F		DOI:11054 / urinary bladder cancer Biomuta	0.21	0	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease/Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
387	387	I387T	rs748303093	Deficiency of acetyl-CoA acetyltransferase ClinVar; Deficiency of acetyl-CoA acetyltransferase DisGeNet; not provided ClinVar; Ketoacidosis DisGeNet; Neurologic Deficits DisGeNet	-2.17	0.08	no			
388	388	G388W		DOI:1324 / lung cancer Biomuta	-0.31	0	no			
388	388	G388E	rs773491386	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.20	0	no			
388	388	G388A		DOI:0070003 / blastoma Biomuta; DOI:3571 / liver cancer Biomuta	-0.53	0	no			
389	389	M389I	rs377295639	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.26	0	no			
390	390	S390P	rs1184088336	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.33	0	no			
397	397	H397Q		DOI:10283 / prostate cancer Biomuta	-0.73	0.02	no			
397	397	H397D	rs746332363	Deficiency of acetyl-CoA acetyltransferase ClinVar	-1.28	0.02	no			
400	400	H400Y	rs201183545	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.04	0.27	yes		no	
400	400	H400R	rs761086326	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.51	0.27	yes		no	
406	406	E406G	rs147872303	Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.71	0.31	yes		no	
407	407	Y407C		DOI:9256 / colorectal cancer Biomuta	-0.94	0.23	yes		no	
408	408	G408V	rs1131691780	not provided ClinVar	1.27	0	no			
408	408	G408R	rs553101581	Deficiency of acetyl-CoA acetyltransferase ClinVar	0.06	0	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Interface (predicted)	Sites/regions
410	410	A410V	rs767412638	Deficiency of acetyl-CoA acetyltransferase ClinVar	0.32	0	no			
416	416	G416E		DOID:4362 / cervical cancer Biomuta	-0.17	0.38	yes	yes	no	
417	417	G417E		DOID:4362 / cervical cancer Biomuta	-0.44	0.01	no			
418	418	G418D	rs886042080	Deficiency of acetyl-CoA acetyltransferase ClinVar; not provided ClinVar	-0.35	0.07	no			
421	421	A421S		DOID:3571 / liver cancer Biomuta	-0.55	0	no			
421	421	A421T		DOID:1793 / pancreatic cancer Biomuta	-0.50	0	no			
421	421	A421V		DOID:0070003 / blastoma Biomuta;	0.26	0	no			
423	423	L423R		DOID:3571 / liver cancer Biomuta	-1.24	0	no			
427	427	L427M		Deficiency of acetyl-CoA acetyltransferase ClinVar	-0.12	0.52	yes		no	

Variants in ACAT1 are derived from different sources including Humsavar, OMIM, ClinVar, Biomuta. Variants are mapped on the PDB file 2IBY, chain A. $\Delta\Delta G$ values are predicted with INPS starting from structure. RSA= Relative Solvent Accessibility computed with DSSP. Surface residues are those with RSA ≥ 0.2 . Residues that are part of the tetrameric interface are computed from the Biological Assembly of 2IBY. Residues in non-tetrameric interfaces are predicted with ISPRED4. Sites and regions are derived from UniProt annotations.

Supplementary Table S4: Variants in ACAT2

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	Δ AG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
3	-	A3S		DOI:11054 / urinary bladder cancer Biomuta						
9	9	V9F		DOI:3571 / liver cancer Biomuta	-0.53	0	no			
13	13	A13V		DOI:3571 / liver cancer Biomuta	0.45	0	no			
15	15	R15L		DOI:3571 / liver cancer Biomuta	0.76	0	no			
21	21	F21L		DOI:4362 / cervical cancer Biomuta	-0.58	0.42	yes	yes	no	
22	22	N22S		DOI:2994 / germ cell cancer Biomuta	0.08	0.72	yes		no	
26	26	A26D		DOI:363 / uterine cancer Biomuta	-0.77	0.22	yes		no	
31	31	Q31H		DOI:363 / uterine cancer Biomuta	-0.61	0.11	no			
34	34	G34A		DOI:0060119 / pharynx cancer Biomuta	0.65	0	no			
42	42	L42F		DOI:1324 / lung cancer Biomuta	-1.12	0.05	no			
49	49	P49L		DOI:363 / uterine cancer Biomuta	-0.46	0.3	yes		no	
				DOI:0070003 / blastoma Biomuta;						
52	52	V52M		DOI:3571 / liver cancer Biomuta	-1.46	0.04	no			
58	58	G58V		DOI:3571 / liver cancer Biomuta	-0.81	0	no			
62	62	A62S		DOI:1324 / lung cancer Biomuta	-0.05	0.42	yes		yes	
73	73	A73S		DOI:3571 / liver cancer Biomuta	-0.59	0	no			
78	78	G78E		DOI:1909 / melanoma Biomuta	-1.15	0.55	yes		no	
80	80	P80S		DOI:1909 / melanoma Biomuta	-0.95	0.32	yes		no	
				DOI:0070003 / blastoma Biomuta;						
83	83	V83F		DOI:3571 / liver cancer Biomuta	-1.78	0.04	no			
93	93	G93W		DOI:3571 / liver cancer Biomuta	-0.25	0.07	no			
106	106	I106M		DOI:1909 / melanoma Biomuta	-1.63	0	no			
108	108	I108V		DOI:3571 / liver cancer Biomuta	0.38	0.75	yes		yes	
113	113	I113M		DOI:1324 / lung cancer Biomuta	-0.43	0.01	no			
121	121	N121H		DOI:1324 / lung cancer Biomuta	-0.23	0.04	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
122	122	M122T		DOID:10534 / stomach cancer Biomuta	-2.18	0.01	no			
134	134	G134E		DOID:263 / kidney cancer Biomuta	-0.06	0.61	yes	yes	yes	
139	139	E139D		DOID:11934 / head and neck cancer Biomuta; DOID:363 / uterine cancer Biomuta	-0.08	0.98	yes	yes	yes	
147	147	L147I		DOID:0070003 / blastoma Biomuta;						
147	147	L147P		DOID:3571 / liver cancer Biomuta	-0.12	0.5	yes		yes	
148	148	C148S		DOID:363 / uterine cancer Biomuta	-0.87	0.5	yes		yes	
153	153	D153G		DOID:0070003 / blastoma Biomuta;						
158	158	C158G		DOID:3571 / liver cancer Biomuta	-0.69	0.02	no			
160	160	M160I		DOID:363 / uterine cancer Biomuta	-1.30	0.17	no			
161	161	G161S		DOID:1793 / pancreatic cancer Biomuta	-0.61	0.1	no	yes		
176	176	E176K	rs371307389	DOID:3070 / malignant glioma Biomuta	-0.22	0	no			
179	179	D179H		Acetyl-CoA acetyltransferase-2 deficiency ClinVar	-0.12	0.6	yes		yes	
184	184	L184V		DOID:0070003 / blastoma Biomuta;						
192	192	A192S		DOID:3571 / liver cancer Biomuta	-0.19	0.02	no			
195	195	A195V		DOID:1612 / breast cancer Biomuta	-1.09	0.48	yes		yes	
195	195	A195S		DOID:3571 / liver cancer Biomuta	-0.90	0.02	no			
197	197	H197R		DOID:0070003 / blastoma Biomuta;						
203	203	V203E		DOID:3571 / liver cancer Biomuta	-1.39	0.59	yes		no	
210	210	R210K		DOID:3070 / malignant glioma Biomuta	-0.49	0.59	yes		no	
				DOID:2531 / hematologic cancer Biomuta	-0.24	0.29	yes		no	
				DOID:1612 / breast cancer Biomuta	-1.38	0.07	no			
				DOID:5041 / esophageal cancer Biomuta	-0.16	0.88	yes		yes	

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	ΔΔG	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
211	211	K211R	rs256683	Polymorphism HUMSAVAR; DOI:9256 / colorectal cancer Biomuta	0.37	0.98	yes	no	no	
219	219	D219Y		DOI:3571 / liver cancer Biomuta	0.72	0.06	no			
219	219	D219H		DOI:9256 / colorectal cancer Biomuta	-0.21	0.06	no			
221	221	F221C		DOI:363 / uterine cancer Biomuta	-1.17	0.26	yes		yes	
237	237	Y237C		DOI:363 / uterine cancer Biomuta	-0.23	0.67	yes		yes	
243	243	T243M		DOI:3070 / malignant glioma Biomuta;						
243	243	T243A		DOI:9256 / colorectal cancer Biomuta	0.22	0.58	yes		yes	
262	262	V262I		DOI:10534 / stomach cancer Biomuta	-0.27	0.58	yes		yes	
270	270	D270N		DOI:363 / uterine cancer Biomuta	-0.34	0	no			
272	272	R272C		DOI:0070003 / blastoma Biomuta	-0.28	0.53	yes		no	
274	274	L274R		DOI:363 / uterine cancer Biomuta	-0.77	0.32	yes		no	
278	278	A278V		DOI:1793 / pancreatic cancer Biomuta	-1.23	0.13	no			
279	279	R279Q		DOI:10534 / stomach cancer Biomuta	-0.04	0	no			
280	280	I280V		DOI:1324 / lung cancer Biomuta	-0.98	0.31	yes		no	
284	284	S284C		DOI:9256 / colorectal cancer Biomuta	-0.58	0.08	no			
286	286	V286A		not provided ClinVar	-0.25	0.01	no			
292	292	I292V		DOI:11054 / urinary bladder cancer Biomuta	-0.35	0.12	no			
300	300	A300T		DOI:9256 / colorectal cancer Biomuta;						
304	304	A304S		DOI:1909 / melanoma Biomuta	-0.38	0.16	no			
310	310	W310L		DOI:1324 / lung cancer Biomuta	-1.09	0	no			
329	329	A329S		DOI:3963 / thyroid carcinoma Biomuta	-1.39	0	no			
335	335	L335V		DOI:3571 / liver cancer Biomuta	-0.33	0.13	no			
335	335	L335V		DOI:9256 / colorectal cancer Biomuta;						
				DOI:1909 / melanoma Biomuta	-0.76	0.17	no			
				DOI:3070 / malignant glioma Biomuta	-1.62	0.13	no			

Position in UniProt	Position in PDB	Variant	dbSNP	Disease Source	$\Delta\Delta G$	RSA	surface	4-meric interface	Non 4-meric interface (predicted)	Sites/regions
336	336	G336R		DOID:11054 / urinary bladder cancer Biomuta	-0.68	0.62	yes		no	
341	341	K341R		DOID:0070003 / blastoma Biomuta;						
358	358	S358F		DOID:3571 / liver cancer Biomuta	-0.76	0.18	no			
				DOID:363 / uterine cancer Biomuta	-0.62	0	no			
				DOID:363 / uterine cancer Biomuta;						
				DOID:9256 / colorectal cancer Biomuta;						
363	363	L363I		DOID:1909 / melanoma Biomuta	-0.45	0	no			
363	363	L363V		DOID:1324 / lung cancer Biomuta	-0.73	0	no			
365	365	T365I		DOID:3070 / malignant glioma Biomuta	0.10	0	no			
371	371	E371Q		DOID:1324 / lung cancer Biomuta	-0.17	0.35	yes		no	
376	376	S376I		DOID:3571 / liver cancer Biomuta	0.01	0.25	yes		no	
				DOID:11934 / head and neck cancer Biomuta; DOID:9256 / colorectal cancer Biomuta; DOID:363 / uterine cancer Biomuta						
377	377	R377C		cancer Biomuta	-0.46	0.31	yes		no	
380	380	A380V		DOID:10534 / stomach cancer Biomuta	0.75	0	no			
				DOID:0070003 / blastoma Biomuta;						
385	385	G385A		DOID:3571 / liver cancer Biomuta	-0.07	0.12	no			
				DOID:0070003 / blastoma Biomuta;						
387	387	G387V		DOID:3571 / liver cancer Biomuta	0.68	0.02	no	yes		
388	388	M388V		DOID:9256 / colorectal cancer Biomuta	-0.40	0.34	yes	yes	yes	
394	394	V394A		DOID:9256 / colorectal cancer Biomuta	-1.19	0	no			
394	394	V394F		DOID:3571 / liver cancer Biomuta	-0.41	0	no			

Variants in ACAT2 are derived from different sources including Humsavar, OMIM, ClinVar, Biomuta. Variants are mapped on the PDB file 1WL4, chain A. $\Delta\Delta G$ values are predicted with INPS starting from structure. RSA= Relative Solvent Accessibility computed with DSSP. Surface residues are those with RSA ≥ 0.2 . Residues that are part of the

tetrameric interface are computed from the Biological Assembly of 1WL4. Residues in non-tetrameric interfaces are predicted with ISPRED4. Sites and regions are derived from UniProt annotations.