



**SUPP. FIGURE S1** Two states of the human pyruvate carboxylase in a rotated version. The figure shows the rotated version of the same structures as in Fig 3. Conformer 1 (left) has its BCCP domain in the vicinity of BC domain, while in the conformer 2 (right) BCCP domain brings biotin to the CT domain. The structures contain four homomonomers, of which monomer C is depicted in the cartoon representation, while three other monomers are in surface representation. The four domains of monomer C are color coded: BC in yellow, CT in green, PT in violet, BCCP in pink. The ligands (ATP, biotin, CoA, pyruvate) are depicted as gray spheres. The novel mutated residues revealed in our study are shown in big colored spheres: for type A PCD the residues are depicted in red, for type C PCD in blue. The variants previously reported in literature are depicted in small colored spheres, either red for type A PCD or blue for type C PCD.

**A**

					Y							
Hs	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Pt	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Mam	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Clf	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Bt	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Mm	264	R	D	C	<b>S</b>	I	Q	R	R	H	Q	273
Rn	263	R	D	C	<b>S</b>	I	Q	R	R	H	Q	272
Dr	265	R	D	C	<b>S</b>	I	Q	R	R	H	Q	274
Dm	265	R	D	C	<b>S</b>	V	Q	R	R	H	Q	274
Ag	264	R	D	C	<b>S</b>	V	Q	R	R	H	Q	273
Ce	258	R	D	C	<b>S</b>	V	Q	R	R	H	Q	267

**B**

						T						
Hs	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Pt	1431	N	W	G	G	<b>A</b>	T	F	D	V	A	1440
Mam	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Clf	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Bt	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Mm	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Rn	606	N	W	G	G	<b>A</b>	T	F	D	V	A	615
Dr	608	N	W	G	G	<b>A</b>	T	F	D	A	A	617
Dm	625	N	W	G	G	<b>A</b>	T	F	D	V	A	634
Ag	624	N	W	G	G	<b>A</b>	T	F	D	V	A	633
Ce	601	N	W	G	G	<b>A</b>	T	F	D	V	S	611

**C**

							Q					
Hs	621	E	C	P	W	R	<b>R</b>	L	Q	E	L	630
Pt	1446	E	C	P	W	R	<b>R</b>	L	Q	E	L	1455
Mam	621	E	C	P	W	R	<b>R</b>	L	Q	E	L	630
Clf	621	E	C	P	W	R	<b>R</b>	L	Q	E	L	630
Bt	621	E	C	P	W	R	<b>R</b>	L	Q	E	L	630
Mm	622	E	C	P	W	R	<b>R</b>	L	Q	E	L	631
Rn	621	E	C	P	W	R	<b>R</b>	L	Q	E	L	630
Dr	623	E	C	P	W	K	<b>R</b>	L	Q	E	L	632
Dm	640	E	C	P	W	E	<b>R</b>	L	E	E	M	649
Ag	639	E	C	P	W	E	<b>R</b>	L	E	E	M	648
Ce	617	E	C	P	W	E	<b>R</b>	L	Q	T	L	626

**D**

								S				
Hs	1076	V	F	F	E	L	N	G	Q	L	R	1085
Pt	1902	V	F	F	E	L	N	G	Q	L	R	1911
Mam	1076	V	F	F	E	L	N	G	Q	L	R	1085
Clf	1076	V	F	F	E	L	N	G	Q	L	R	1085
Bt	1076	V	F	F	E	L	N	G	Q	L	R	1085
Mm	1077	V	F	F	E	L	N	G	Q	L	R	1086
Rn	1076	V	F	F	E	L	N	G	Q	L	R	1085
Dr	1077	V	F	F	E	L	N	G	Q	L	R	1086
Dm	1095	V	F	F	E	L	N	G	Q	L	R	1104
Ag	1094	V	F	F	E	L	N	G	Q	L	R	1103
Ce	1072	V	F	F	D	L	N	G	Q	M	R	1081

**SUPP. FIGURE S2** Comparative analysis of amino acid residues of pyruvate carboxylase among different species. In five of six patients from our study, four punctiform allelic variants cause single amino acid changes. The affected wild-type residue is depicted in bold and the mutated residue in black above the human wild-type residue. The specific mutations are: serine 266 into tyrosine (**A**), alanine 610 into threonine (**B**), arginine 626 into glutamine (**C**), asparagine 1081 into serine (**D**). Abbreviations: Hs for *Homo sapiens*, Pt for *Pan troglodytes*, Mam for *Macaca mulatta*, Clf for *Canis lupus familiaris*, Bt for *Bos taurus*, Mm for *Mus musculus*, Rn for *Rattus norvegicus*, Dr for *Danio rerio*, Dm for *Drosophila melanogaster*, Ag for *Anopheles gambiae*, Ce for *Caenorhabditis elegans* (from NCBI HomoloGene browser)