Supplementary Table 1. *DPP8* LoF variants in TCGA. Simple somatic mutation (SSM) affected frequency is calculated as the number of cases affected by a specific mutation in a TCGA disease project divided by the number of cases tested for SSM in that disease project in TCGA. ins = insertion. del = deletion. * Premature termination codon (PTC).

Position	Reference	Alternate	Protein consequence	Annotation	Case ID	Disease	Number of SSM affected cases and frequency
65479016delA			p.Gln458Lys*29	Frameshift	TCGA-AZ-6598 TCGA-AD-5900	Colon Adenocarcinoma	2/400 (0.50%)
65479011_65479012insG			p.Gln458Pro*8	Frameshift	TCGA-HU-A4GT	Stomach Adenocarcinoma	1/440 (0.23%)
65474260delC			p.Ile512*	Frameshift	TCGA-12-0778	Glioblastoma Multiforme	1/393 (0.25%)
65467180_65467181insAGGTAAATTATTAGTCAATT			p.Thr543Lys*13	Frameshift	TCGA-13-1500	Ovarian Serous Cystadenocarcinoma	1/463 (0.23%)
65456248_65456249insAAATTTAAGCCCTCGGTGACAGGATCCCCTGTTGAGGGCTTAAATTTGAAGGCGCCTTT			p.Glu715Lys*31	Frameshift	TCGA-4V-A9QI	Thymoma	1/123 (0.81%)
65454301delAGAGGTATCC			p.Gly758Pro*2	Frameshift	TCGA-AP-A1DO	Uterine Corpus Endometrial Carcinoma	1/530 (0.19%)
65500743	C	A	p.Glu153*	Stop gained	TCGA-BK-A6W3	Uterine Corpus Endometrial Carcinoma	1/530 (0.19%)
65500731	C	A	p.Glu157*	Stop gained	TCGA-D1-A17Q	Uterine Corpus Endometrial Carcinoma	1/530 (0.19%)

65500639	A	T	p.Tyr187*	Stop gained	TCGA-VQ-A91D	Stomach Adenocarcinoma	1/440 (0.23%)
65490237	C	A	p.Glu276*	Stop gained	TCGA-AX-A05Z	Uterine Corpus	2/530 (0.38%)
					TCGA-AJ-A5DW	Endometrial Carcinoma	
							1/400 (0.25%)
					TCGA-AA-3510	Colon Adenocarcinoma	
65480371	G	A	p.Gln399*	Stop gained	TCGA-D3-A8GK	Skin Cutaneous	1/469 (0.21%)
						Melanoma	
65478907	G	A	p.Arg493*	Stop gained	TCGA-AG-A02N	Rectum Adenocarcinoma	1/137 (0.73%)
65467149	G	C	p.Tyr553*	Stop gained	TCGA-Q1-A6DW	Cervical Squamous Cell	1/289 (0.35%)
						Carcinoma and	
						Endocervical	
						Adenocarcinoma	
65467135_65467136insTTGTCATC			p.Val558A*6	Stop gained	TCGA-24-1431	Ovarian Serous	1/436 (0.23%)
CACCTACCTCGG						Cystadenocarcinoma	
65467124	C	A	p.Glu562*	Stop gained	TCGA-29-1768	Ovarian Serous	1/436 (0.23%)
						Cystadenocarcinoma	
65456263	G	A	p.Arg710*	Stop gained	TCGA-AZ-4615	Colon Adenocarcinoma	1/400 (0.25%)
65454394	G	A	p.Gln730*	Stop gained	TCGA-ZP-A9CY	Liver Hepatocellular	1/364 (0.27%)
						Carcinoma	

Supplementary Table 2. *DPP8* LoF variants in COSMIC. Nonsense mutation is a substitution mutation resulting in a premature termination codon (*). CDS = coding sequence; AA = amino acid, SSM = simple somatic mutation.

CDS mutation	AA mutation	Legacy mutation ID	Type	Disease	Number of SSM affected cases
c.2262G>A	p.Trp754*	COSM5946730	Nonsense	Lymphoid neoplasm	1
c.2017C>T	p.Gln673*	COSM6574976	Nonsense	ER-PR-positive breast carcinoma	1
c.1659C>G	p.Tyr553*	COSM4856031	Nonsense	Cervical squamous cell carcinoma	1
c.328G>T	p.Glu110*	COSM1678543	Nonsense	Colon adenocarcinoma	2
c.2128C>T	p.Arg710*	COSM3690497	Nonsense	Colon adenocarcinoma	1
c.826G>T	p.Glu276*	COSM964071	Nonsense	Endometrioid carcinoma Colon adenocarcinoma	3
c.1477C>T	p.Arg493*	COSM167000	Nonsense	Colon adenocarcinoma	1
c.2170C>T	p.Gln724*	COSM6648997	Nonsense	Colon adenocarcinoma	1
c.457G>T	p.Glu153*	COSM8970383	Nonsense	Endometrioid carcinoma	1
c.469G>T	p.Glu157*	COSM964073	Nonsense	Endometrioid carcinoma	1
c.2188C>T	p.Gln730*	COSM8423812	Nonsense	Hepatocellular carcinoma	1
c.2649C>G	p.Tyr883*	COSM88480	Nonsense	Ovarian clear cell carcinoma	1
c.1684G>T	p.Glu562*	COSM1323886	Nonsense	Ovarian serous carcinoma	1
c.1816G>T	p.Glu606*	COSM3981612	Nonsense	Ovarian mixed adeno-squamous carcinoma	1
c.2218C>T	p.Arg740*	COSM5929565	Nonsense	Skin basal cell carcinoma	1
c.1927G>T	p.Gly643*	COSM7894053	Nonsense	Malignant melanoma	1
c.1195C>T	p.Gln399*	COSM8050061	Nonsense	Malignant melanoma	1
c.1228G>T	p.Glu410*	COSM7945996	Nonsense	Malignant melanoma	1
c.2352G>A	p.Trp784*	COSM135677	Nonsense	Skin squamous cell carcinoma	1
c.561T>A	p.Tyr187*	COSM8209774	Nonsense	Stomach adenocarcinoma	1

Supplementary Table 3. Genome-wide significant loci for severe COVID-19: Intronic *DPP9* variants rs12610495 and rs2109069. hg19_coordinates: the hg19 chromosome position. Hg38_coordinates: the hg38 chromosome position. a1: the effect allele (aligned to the + strand). a2: the non-effect allele (aligned to the + strand). afr/amr/eas/eur/sas: the allele frequency for A1 in AFR/AMR/EAS/EUR/SAS population in 1000 Genomes. beta: association between the trait and the SNP expressed per additional copy of the effect allele (odds ratio is given on the log-scale). efo: the experimental factor oncology term for the phenotype or disease. AFR = African; AMR = American; EAS = East Asian; EUR = European; SAS = South Asian.

		Genomic location				Allele frequencies											
Gene	**rsid**	**hg19_coordinates**	**hg38_coordinates**	**a1**	**a2**	**afr**	**amr**	**eas**	**eur**	**sas**	**beta**	**Standard error of beta**	***p* value**	**Number of individuals**	**Dataset ID**	**Trait (phenotype or disease)**	***p* value COVID**	**efo**
DPP9	rs12610495	chr19:4717672	chr19:4717660	A	G	0.872	0.797	0.857	0.706	0.828	NA	NA	1.68E-12	47644	GRASP	Fibrotic idiopathic interstitial pneumonias pulmonary fibrosis	5.20E-06	NCIT_C35714
DPP9	rs12610495	chr19:4717672	chr19:4717660	A	G	0.872	0.797	0.857	0.706	0.828	-0.255	0.0362	2.00E-12	-	NHGRI-EBI_GWAS_Catalog	Interstitial lung disease	5.20E-06	EFO_0004244
DPP9	rs2109069	chr19:4719443	chr19:4719431	A	G	0.196	0.219	0.14	0.321	0.186	NA	NA	2.42E-11	47644	GRASP	Fibrotic idiopathic interstitial pneumonias pulmonary fibrosis	2.41E-05	NCIT_C35714

Supplementary Table 4. The LIHC/HCC (n = 360) and UCEC (n = 540) patient demographics

Characteristic	LIHC/HCC Number and percentage or median and range *	UCEC Number and percentage or median and range *
Sex		
Male	244 (67.8%)	/
Female	116 (32.2%)	540 (100%)
Age at diagnosis (years)	61 (16, 85)	64 (31, 90)
Tumour site		
Liver	360 (100%)	
Endometrium		525 (97.2%)
Fundus uteri		6 (1.11%)
Corpus uteri		4 (0.74%)
Isthmus uteri		3 (0.56%)
Overall death	126 (35%)	91 (16.9%)
Follow up time (days)	587 (1, 3675)	885 (0, 6859)
AJCC stage		
I	169 (46.9%)	334 (61.9%)
II	83 (23.1%)	52 (9.6%)
III	83 (23.1%)	123 (22.8%)
IV	4 (1.11%)	29 5.4%)

*Missing data excluded in percentage calculation

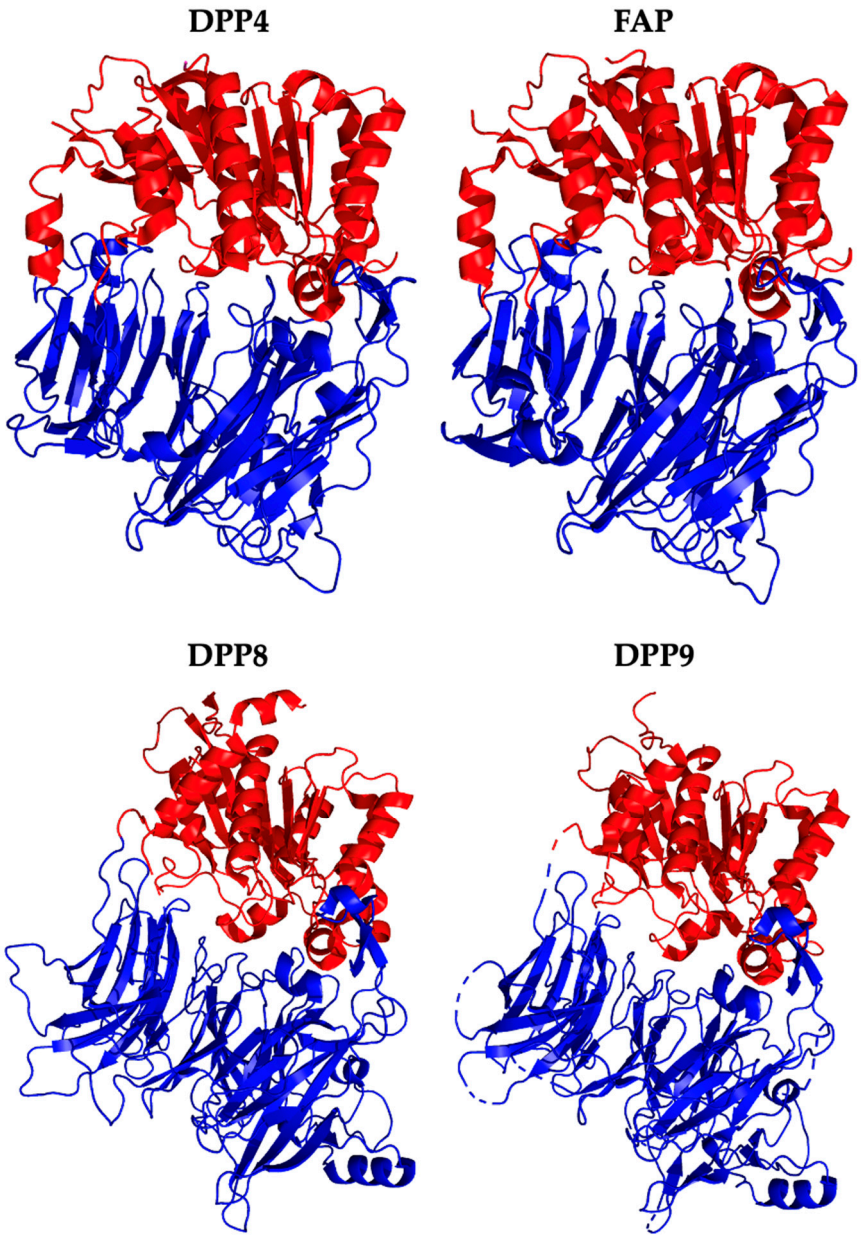
Supplementary Table 5. Cox proportional hazards model with gender as the covariate to evaluate associations between DPP9 expression and survival. HR = hazard ratio; CI = confidence interval.

Variable	Multivariate cox P	HR (CI)
DPP9	0.97	0.99 (0.69-1.41)
Gender	0.3	0.82 (0.57-1.19)

Supplementary Table 6. Cox proportional hazards model with BMI as the covariate to evaluate associations between DPP9 expression and survival. HR = hazard ratio; CI = confidence interval.

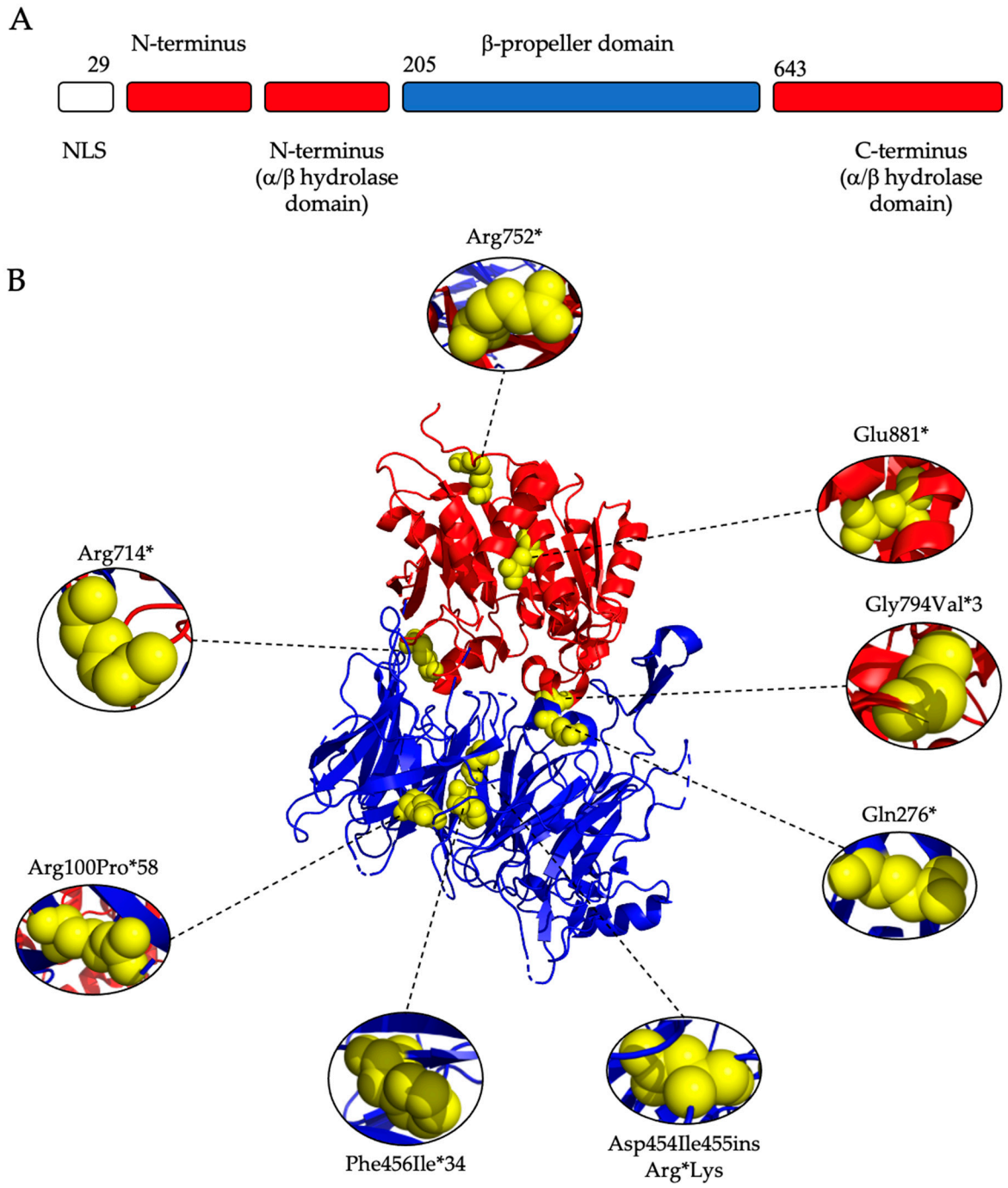
Variable	Multivariate cox P	HR (CI)
DPP9	0.55	1.54 (0.71-3.35)
Overweight	0.7	0.96 (0.8-1.15)
DPP9	0.27	0.75 (0.3-1.89)
Obese/Extreme obese	0.98	0.99 (0.7-1.29)

A



B

Supplementary Figure 1. Crystal structure and protein sequence of the four enzymatic members in the DPP4 gene family. **(A)** Crystal structure of DPP4, FAP, DPP8 and DPP9. Structures were modified and prepared using PyMOL (Version 2.4.2). **(B)** Multiple-sequence alignment of DPP4 (P27487), FAP (Q12884), DPP8 (Q6V1X1) and the long form of DPP9 (Q86TI2-2). Protein sequences were download from UniProt Consortium and alignment was created using Clustal Omega. . = similar; : = highly similar; * = identical.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NLS
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C-terminus
(α/β hydrolase
domain)
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Gln276*
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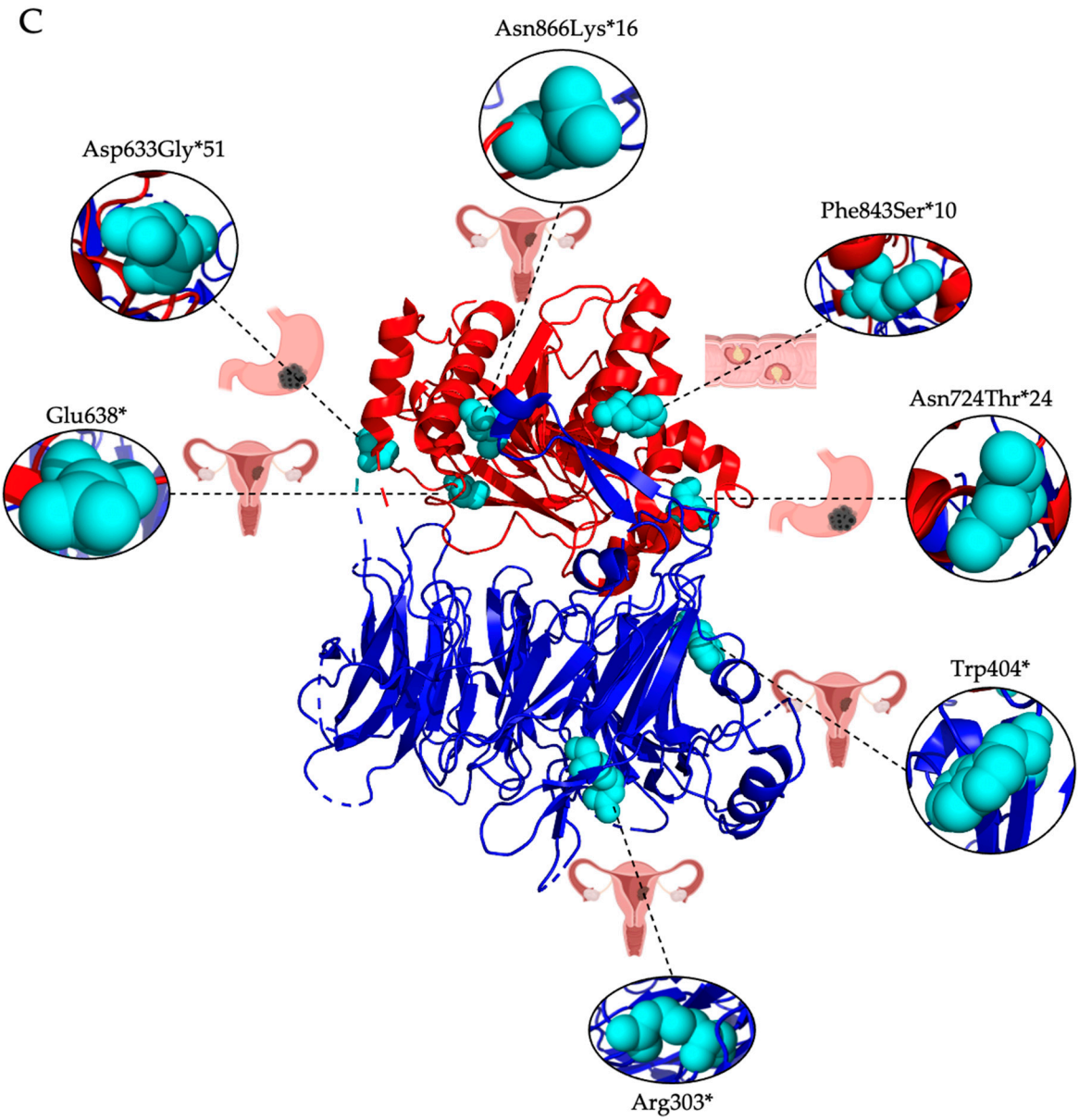
Arg*Lys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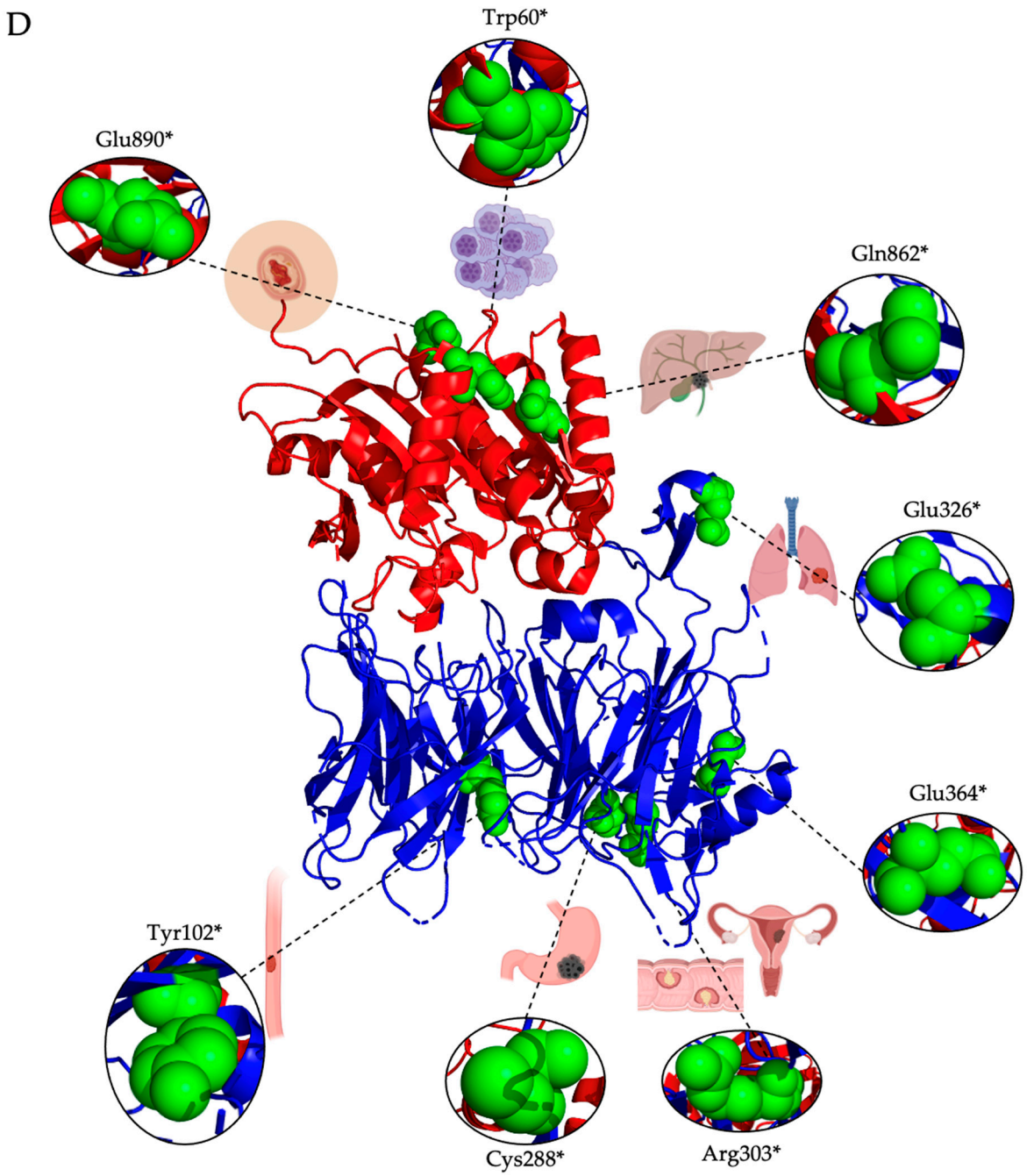
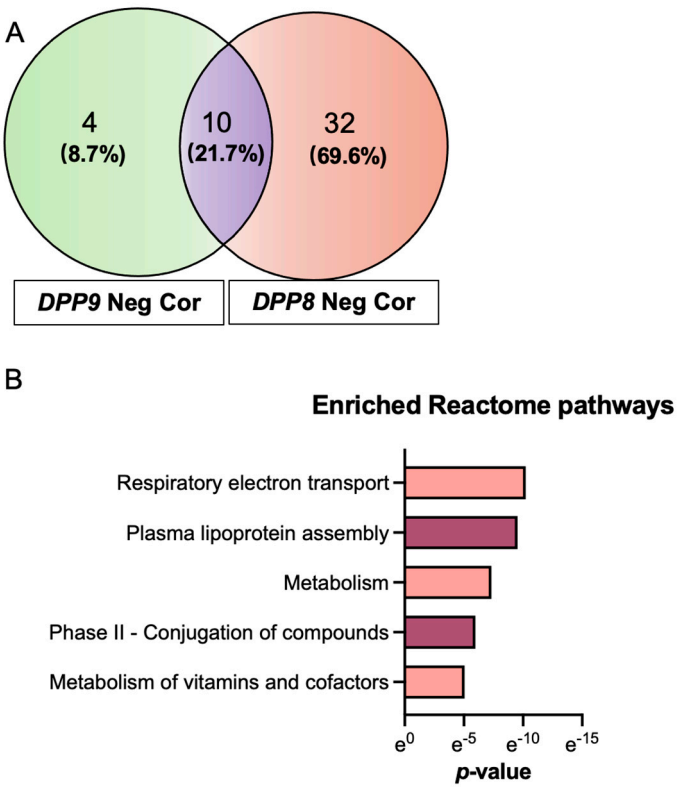
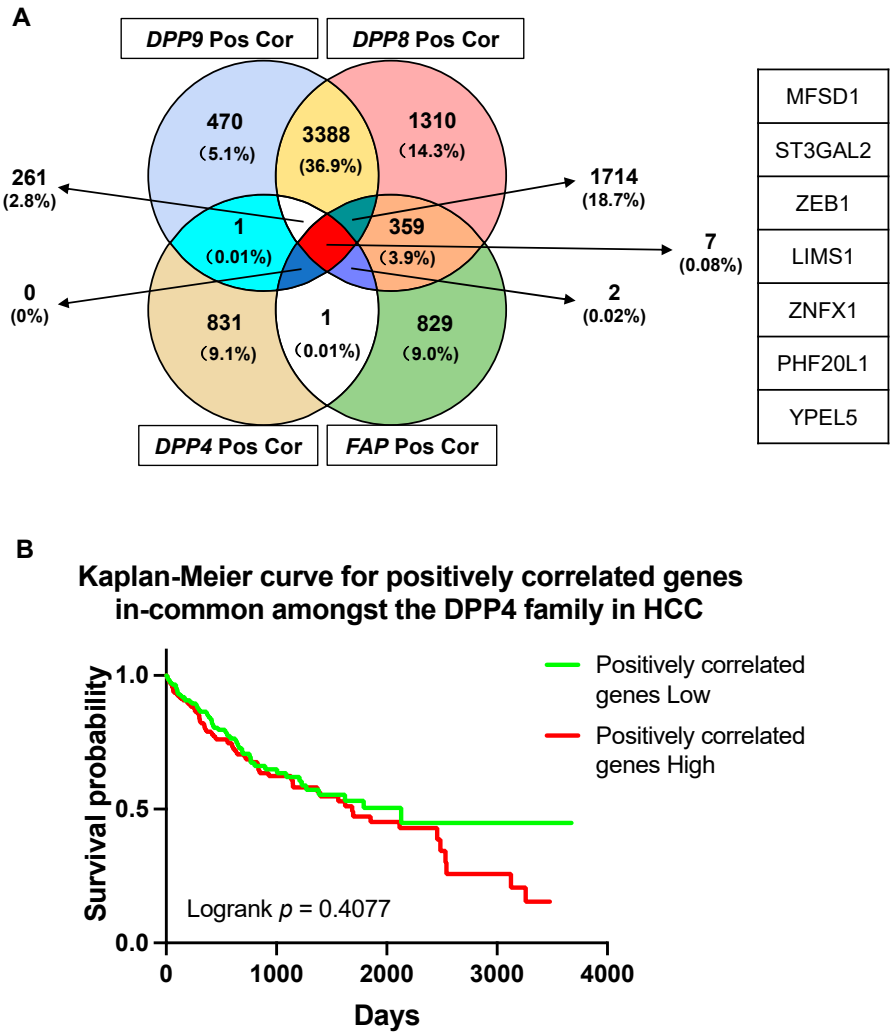


Supplementary Figure 2. *DPP9* variants mapped to the DPP9 protein structure. **(A)** DPP9 protein domain organization. Exonic variants were exported from **(B)** gnomAD, **(C)** TCGA and **(D)** COSMIC databases. The PDB for DPP9 apo structure used here is 6EOQ. The figures were created using PyMOL (Version 2.4.2, Schrödinger, LLC) and BioRender.com. ins = insertion. * Premature termination codon. NLS = nuclear localisation sequence.



Supplementary Figure 3. Enriched Reactome pathways of genes that were negatively correlated and in-common between *DPP9* and *DPP8*. **(A)** Venn diagram of the genes negatively correlated with *DPP9* and *DPP8*. "Neg Cor" refers to negative correlation. **(B)** Enriched Reactome pathways associated with negatively correlated genes in-common between *DPP9* and *DPP8*. This analysis was performed in ConsensusPathDB, where statistical significance, shown as *p* value, was calculated hypergeometrically based on the number of entities in the predefined set and the 10 negatively correlated genes defined in the Venn diagram.



Supplementary Figure 4. Survival analysis on genes that were positively correlated and in-common amongst *DPP9*, *DPP8*, *DPP4* and *FAP* in HCC. **(A)** Venn diagram showing the numbers of genes that were positively correlated in-common with *DPP9*, *DPP8*, *DPP4* and *FAP*. The 7 genes in-common genes with all four genes are listed to the right-hand side. The genes in the blue section and pink section are *TPRA1* and *SH3BP5* respectively. The two genes on the purple section are *VAMP3* and *TTL*. "Pos Cor" refers to positive correlation. **(B)** Kaplan-Meier curve for the 7 genes that were positively correlated in-common amongst *DPP9*, *DPP8*, *DPP4* and *FAP* in HCC patients. The high (red) and low (green) mRNA expression levels of genes in liver tumours were stratified based on median expression value. *p* values were calculated by logrank (Mantel-Cox) test.