

SUPPLEMENTAL MATERIAL

Supplemental Table 1. **List of all the proteins included in the analysis.** A total of 280 proteins have been included in the prediction of the mechanism of action of empagliflozin. Each protein has a Uniprot ID code associated to standardize the nomenclature.

MOTIVE NAME	Uniprot	Display d Name	Protein name
Retention of sodium (hypertension)	P37088	SCNNA	Amiloride-sensitive sodium channel subunit alpha
Retention of sodium (hypertension)	P51168	SCNNB	Amiloride-sensitive sodium channel subunit beta
Retention of sodium (hypertension)	P51172	SCNND	Amiloride-sensitive sodium channel subunit delta
Retention of sodium (hypertension)	P51170	SCNNG	Amiloride-sensitive sodium channel subunit gamma
Retention of sodium (hypertension)	P08235	MCR	Mineralocorticoid receptor
Retention of sodium (hypertension)	P28845	DHI1	Corticosteroid 11-beta-dehydrogenase isozyme 1
Retention of sodium (hypertension)	P80365	DHI2	Corticosteroid 11-beta-dehydrogenase isozyme 2
Retention of sodium (hypertension)	P00797	RENI	Renin

Retention of sodium (hypertension)	P12821	ACE	Angiotensin-converting enzyme
Retention of sodium (hypertension)	P19099	C11B2	Cytochrome P450 11B2, mitochondrial
Retention of sodium (hypertension)	P01160	ANF	Atrial natriuretic factor
Retention of sodium (hypertension)	P25101	EDNRA	Endothelin-1 receptor
Retention of sodium (hypertension)	P05305	EDN1	Endothelin-1
Retention of sodium (hypertension)	P24530	EDNRB	Endothelin B receptor
Retention of sodium (hypertension)	P54710	ATNG	Sodium/potassium-transporting ATPase subunit gamma
Retention of sodium (hypertension)	P05026	AT1B1	Sodium/potassium-transporting ATPase subunit beta-1
Retention of sodium (hypertension)	P50993	AT1A2	Sodium/potassium-transporting ATPase subunit alpha-2
Retention of sodium (hypertension)	P14415	AT1B2	Sodium/potassium-transporting ATPase subunit beta-2
Retention of sodium (hypertension)	P51800	CLCKA	Chloride channel protein ClC-Ka
Retention of sodium (hypertension)	P51801	CLCKB	Chloride channel protein ClC-Kb
Retention of sodium (hypertension)	P55017	S12A3	Solute carrier family 12 member 3
Retention of sodium (hypertension)	Q8WZ55	BSND	Barttin
Retention of sodium (hypertension)	Q9H4A3	WNK1	Serine/threonine-protein kinase WNK1
Retention of sodium (hypertension)	Q96J92	WNK4	Serine/threonine-protein kinase WNK4
Retention of sodium (hypertension)	Q13621	S12A1	Solute carrier family 12 member 1
Retention of sodium (hypertension)	P05019	IGF1	Insulin-like growth factor I
Retention of sodium (hypertension)	P46934	NEDD4	E3 ubiquitin-protein ligase NEDD4

Retention of sodium (hypertension)	O00141	SGK1	Serine/threonine-protein kinase Sgk1
Retention of sodium (hypertension)	Q9HBY8	SGK2	Serine/threonine-protein kinase Sgk2
Retention of sodium (hypertension)	Q96BR1	SGK3	Serine/threonine-protein kinase Sgk3
Retention of sodium (hypertension)	P21728	DRD1	D(1A) dopamine receptor
Retention of sodium (hypertension)	P21918	DRD5	D(1B) dopamine receptor
Retention of sodium (hypertension)	P35462	DRD3	D(3) dopamine receptor
Retention of sodium (hypertension)	P30518	V2R	Vasopressin V2 receptor
Retention of sodium (hypertension)	P47901	V1BR	Vasopressin V1b receptor
Retention of sodium (hypertension)	P37288	V1AR	Vasopressin V1a receptor
Retention of sodium (hypertension)	P16860	ANFB	Natriuretic peptides B
Retention of sodium (hypertension)	P48048	KCNJ1	ATP-sensitive inward rectifier potassium channel 1
Retention of sodium (hypertension)	P13569	CFTR	Cystic fibrosis transmembrane conductance regulator
Retention of sodium (hypertension)	P55011	S12A2	Solute carrier family 12 member 2
Retention of sodium (hypertension)	O14649	KCNK3	Potassium channel subfamily K member 3
Retention of sodium (hypertension)	Q9NPC2	KCNK9	Potassium channel subfamily K member 9
Retention of sodium (hypertension)	P19634	SL9A1	Sodium/hydrogen exchanger 1
Retention of sodium (hypertension)	P48764	SL9A3	Sodium/hydrogen exchanger 3
Decreased renal excretion of uric acid (hyperuricemia)	Q9NRM0	GTR9	Solute carrier family 2 (Glucose transporter type 9) (GLUT-9)
Decreased renal excretion of uric acid (hyperuricemia)	Q9UNQ0	ABCG2	ATP-binding cassette sub-family G member 2

Decreased renal excretion of uric acid (hyperuricemia)	P07911	UROM	Uromodulin (Tamm-Horsfall urinary glycoprotein) (THP)
Decreased renal excretion of uric acid (hyperuricemia)	Q96S37	S22AC	Solute carrier family 22 member 12
Decreased renal excretion of uric acid (hyperuricemia)	Q9NSA0	S22AB	Solute carrier family 22 member 11
Decreased renal excretion of uric acid (hyperuricemia)	Q13113	PDZ1I	PDZK1-interacting protein 1
Decreased renal excretion of uric acid (hyperuricemia)	O14745	NHRF1	Na(+)/H(+) exchange regulatory cofactor NHE-RF1
Decreased renal excretion of uric acid (hyperuricemia)	O00476	NPT4	Sodium-dependent phosphate transport protein 4 (Na(+))
Decreased renal excretion of uric acid (hyperuricemia)	Q8N695	SC5A8	Sodium-coupled monocarboxylate transporter 1
Decreased renal excretion of uric acid (hyperuricemia)	Q1EHB4	SC5AC	Sodium-coupled monocarboxylate transporter 2
Decreased renal excretion of uric acid (hyperuricemia)	Q8TCC7	S22A8	Solute carrier family 22 member 8 (Organic anion transporter 3)
Decreased renal excretion of uric acid (hyperuricemia)	Q4U2R8	S22A6	Solute carrier family 22 member 6
Decreased renal excretion of uric acid (hyperuricemia)	O15439	MRP4	Multidrug resistance-associated protein 4

Decreased renal excretion of uric acid (hyperuricemia)	Q8WWT9	S13A3	Solute carrier family 13 member 3
Decreased renal excretion of uric acid (hyperuricemia)	Q13183	S13A2	Solute carrier family 13 member 2
Hyperphagia and dysregulated appetite (obesity)	P01258	CALC	Calcitonin
Hyperphagia and dysregulated appetite (obesity)	P06881	CALCA	Calcitonin gene-related peptide 1
Hyperphagia and dysregulated appetite (obesity)	P10092	CALCB	Calcitonin gene-related peptide 2
Hyperphagia and dysregulated appetite (obesity)	Q16602	CALRL	Calcitonin gene-related peptide type 1 receptor
Hyperphagia and dysregulated appetite (obesity)	P30988	CALCR	Calcitonin receptor
Hyperphagia and dysregulated appetite (obesity)	P08949	NMB	Neuromedin-B
Hyperphagia and dysregulated appetite (obesity)	P28336	NMBR	Neuromedin-B receptor
Hyperphagia and dysregulated appetite (obesity)	P47871	GLR	Glucagon receptor
Hyperphagia and dysregulated appetite (obesity)	P01308	INS	Insulin

Hyperphagia and dysregulated appetite (obesity)	P06213	INSR	Insulin receptor
Hyperphagia and dysregulated appetite (obesity)	P04118	COL	Colipase
Hyperphagia and dysregulated appetite (obesity)	P30874	SSR2	Somatostatin receptor type 2
Hyperphagia and dysregulated appetite (obesity)	Q92847	GHSR	Growth hormone secretagogue receptor type 1
Hyperphagia and dysregulated appetite (obesity)	P10082	PYY	Peptide YY
Hyperphagia and dysregulated appetite (obesity)	Q9UBC7	GALP	Galanin-like peptide
Hyperphagia and dysregulated appetite (obesity)	O43603	GALR2	Galanin receptor type 2
Hyperphagia and dysregulated appetite (obesity)	P22466	GALA	Galanin peptides [
Hyperphagia and dysregulated appetite (obesity)	P47211	GALR1	Galanin receptor type 1
Hyperphagia and dysregulated appetite (obesity)	Q8NG41	NPB	Neuropeptide B
Hyperphagia and dysregulated appetite (obesity)	Q8N729	NPW	Neuropeptide W

Hyperphagia and dysregulated appetite (obesity)	P48145	NPBW1	Neuropeptides B/W receptor type 1
Hyperphagia and dysregulated appetite (obesity)	P28335	5HT2C	5-hydroxytryptamine receptor 2C
Hyperphagia and dysregulated appetite (obesity)	Q16568	CART	Cocaine- and amphetamine-regulated transcript protein
Hyperphagia and dysregulated appetite (obesity)	Q07869	PPARA	Peroxisome proliferator-activated receptor alpha
Hyperphagia and dysregulated appetite (obesity)	Q8NER1	TRPV1	Transient receptor potential cation channel subfamily V member 1
Hyperphagia and dysregulated appetite (obesity)	Q6IQ20	NAPEP	N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D
Hyperphagia and dysregulated appetite (obesity)	P16671	CD36	Platelet glycoprotein 4
Hyperphagia and dysregulated appetite (obesity)	O00253	AGRP	Agouti-related protein
Hyperphagia and dysregulated appetite (obesity)	Q01726	MSHR	Melanocyte-stimulating hormone receptor (Melanocortin receptor 1)
Hyperphagia and dysregulated appetite (obesity)	P28223	5HT2A	5-hydroxytryptamine receptor 2A (Serotonin receptor 2A)
Hyperphagia and dysregulated appetite (obesity)	P28221	5HT1D	5-hydroxytryptamine receptor 1D

Hyperphagia and dysregulated appetite (obesity)	Q13224	NMDE2	Glutamate receptor ionotropic
Hyperphagia and dysregulated appetite (obesity)	P21964	COMT	Catechol O-methyltransferase
Hyperphagia and dysregulated appetite (obesity)	P14416	DRD2	D(2) dopamine receptor
Hyperphagia and dysregulated appetite (obesity)	P25929	NPY1R	Neuropeptide Y receptor type 1
Hyperphagia and dysregulated appetite (obesity)	Q15761	NPY5R	Neuropeptide Y receptor type 5
Hyperphagia and dysregulated appetite (obesity)	P49146	NPY2R	Neuropeptide Y receptor type 2
Hyperphagia and dysregulated appetite (obesity)	P42785	PCP	Lysosomal Pro-X carboxypeptidase
Hyperphagia and dysregulated appetite (obesity)	Q13258	PD2R	Prostaglandin D2 receptor
Hyperphagia and dysregulated appetite (obesity)	P35408	PE2R4	Prostaglandin E2 receptor EP4 subtype
Hyperphagia and dysregulated appetite (obesity)	Q9HD89	RETN	Resistin
Hyperphagia and dysregulated appetite (obesity)	P20396	TRH	Pro-thyrotropin-releasing hormone

Hyperphagia and dysregulated appetite (obesity)	O75882	ATRN	Attractin (Mahogany homolog)
Hyperphagia and dysregulated appetite (obesity)	P43220	GLP1R	Glucagon-like peptide 1 receptor
Hyperphagia and dysregulated appetite (obesity)	P42127	ASIP	Agouti-signaling protein (ASP) (Agouti switch protein)
Hyperphagia and dysregulated appetite (obesity)	P41145	OPRK	Kappa-type opioid receptor
Hyperphagia and dysregulated appetite (obesity)	P41143	OPRD	Delta-type opioid receptor
Hyperphagia and dysregulated appetite (obesity)	P41146	OPRX	Nociceptin receptor
Hyperphagia and dysregulated appetite (obesity)	P01031	CO5	Complement C5
Hyperphagia and dysregulated appetite (obesity)	P06307	CCKN	Cholecystokinin
Hyperphagia and dysregulated appetite (obesity)	P32239	GASR	Gastrin/cholecystokinin type B receptor
Hyperphagia and dysregulated appetite (obesity)	P32238	CCKAR	Cholecystokinin receptor type A
Hyperphagia and dysregulated appetite (obesity)	P10997	IAPP	Islet amyloid polypeptide (Amylin)

Hyperphagia and dysregulated appetite (obesity)	P32247	BRS3	Bombesin receptor subtype-3
Hyperphagia and dysregulated appetite (obesity)	P01275	GLUC	Glucagon
Hyperphagia and dysregulated appetite (obesity)	P06727	APOA4	Apolipoprotein A-IV
Hyperphagia and dysregulated appetite (obesity)	P41159	LEP	Leptin
Hyperphagia and dysregulated appetite (obesity)	P48357	LEPR	Leptin receptor
Hyperphagia and dysregulated appetite (obesity)	P20382	MCH	Pro-MCH
Hyperphagia and dysregulated appetite (obesity)	Q99705	MCHR1	Melanin-concentrating hormone receptor 1
Hyperphagia and dysregulated appetite (obesity)	Q9UBU3	GHRL	Appetite-regulating hormone
Hyperphagia and dysregulated appetite (obesity)	P01303	NPY	Pro-neuropeptide Y
Hyperphagia and dysregulated appetite (obesity)	P83859	OX26	Orexigenic neuropeptide QRFP
Hyperphagia and dysregulated appetite (obesity)	Q96P65	QRFP	Pyroglutamylated RFamide peptide receptor

Hyperphagia and dysregulated appetite (obesity)	P50391	NPY4R	Neuropeptide Y receptor type 4
Hyperphagia and dysregulated appetite (obesity)	P32245	MC4R	Melanocortin receptor 4
Hyperphagia and dysregulated appetite (obesity)	P41968	MC3R	Melanocortin receptor 3
Hyperphagia and dysregulated appetite (obesity)	P21554	CNR1	Cannabinoid receptor 1
Hyperphagia and dysregulated appetite (obesity)	O00519	FAAH1	Fatty-acid amide hydrolase 1
Hyperphagia and dysregulated appetite (obesity)	P48546	GIPR	Gastric inhibitory polypeptide receptor
Hyperphagia and dysregulated appetite (obesity)	O60674	JAK2	Tyrosine-protein kinase JAK2
Hyperphagia and dysregulated appetite (obesity)	P03372	ESR1	Estrogen receptor
Hyperphagia and dysregulated appetite (obesity)	P54646	AAPK2	5'-AMP-activated protein kinase catalytic subunit alpha-2
Hyperphagia and dysregulated appetite (obesity)	P23560	BDNF	Brain-derived neurotrophic factor (Abrineurin)
Hyperphagia and dysregulated appetite (obesity)	Q16620	NTRK2	BDNF/NT-3 growth factors receptor

Hyperphagia and dysregulated appetite (obesity)	P31645	SC6A4	Sodium-dependent serotonin transporter
Hyperphagia and dysregulated appetite (obesity)	P08913	ADA2A	Alpha-2A adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P18825	ADA2C	Alpha-2C adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P18089	ADA2B	Alpha-2B adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P35348	ADA1A	Alpha-1A adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P35368	ADA1B	Alpha-1B adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P08588	ADRB1	Beta-1 adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P25100	ADA1D	Alpha-1D adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P07550	ADRB2	Beta-2 adrenergic receptor
Hyperphagia and dysregulated appetite (obesity)	P06850	CRF	Corticoliberin
Hyperphagia and dysregulated appetite (obesity)	P30559	OXYR	Oxytocin receptor (OT-R)

Hyperphagia and dysregulated appetite (obesity)	P01213	PDYN	Proenkephalin-B
Hyperphagia and dysregulated appetite (obesity)	P14867	GBRA1	Gamma-aminobutyric acid receptor subunit alpha-1
Hyperphagia and dysregulated appetite (obesity)	P35372	OPRM	Mu-type opioid receptor
Hyperphagia and dysregulated appetite (obesity)	P31644	GBRA5	Gamma-aminobutyric acid receptor subunit alpha-5
Hyperphagia and dysregulated appetite (obesity)	P48169	GBRA4	Gamma-aminobutyric acid receptor subunit alpha-4
Hyperphagia and dysregulated appetite (obesity)	Q16445	GBRA6	Gamma-aminobutyric acid receptor subunit alpha-6
Hyperphagia and dysregulated appetite (obesity)	P47869	GBRA2	Gamma-aminobutyric acid receptor subunit alpha-2
Hyperphagia and dysregulated appetite (obesity)	P34903	GBRA3	Gamma-aminobutyric acid receptor subunit alpha-3
Hyperphagia and dysregulated appetite (obesity)	P28472	GBRB3	Gamma-aminobutyric acid receptor subunit beta-3
Hyperphagia and dysregulated appetite (obesity)	P47870	GBRB2	Gamma-aminobutyric acid receptor subunit beta-2
Hyperphagia and dysregulated appetite (obesity)	P18505	GBRB1	Gamma-aminobutyric acid receptor subunit beta-1

Hyperphagia and dysregulated appetite (obesity)	P35367	HRH1	Histamine H1 receptor
Hyperphagia and dysregulated appetite (obesity)	P01189	COLI	Pro-opiomelanocortin (POMC)
Hyperphagia and dysregulated appetite (obesity)	P34972	CNR2	Cannabinoid receptor 2
Hyperphagia and dysregulated appetite (obesity)	P42345	MTOR	Serine/threonine-protein kinase mTOR
Hyperphagia and dysregulated appetite (obesity)	P01266	THYG	Thyroglobulin (Tg)
Hyperphagia and dysregulated appetite (obesity)	P29120	NEC1	Neuroendocrine convertase 1
Hyperphagia and dysregulated appetite (obesity)	Q9NRF2	SH2B1	SH2B adapter protein 1
Hyperphagia and dysregulated appetite (obesity)	P81133	SIM1	Single-minded homolog 1
Hyperphagia and dysregulated appetite (obesity)	Q9BXC9	BBS2	Bardet-Biedl syndrome 2 protein
Hyperphagia and dysregulated appetite (obesity)	Q96RK4	BBS4	Bardet-Biedl syndrome 4 protein
Hyperphagia and dysregulated appetite (obesity)	Q9NPJ1	MKKS	McKusick-Kaufman/Bardet-Biedl syndromes putative chaperonin

Hyperphagia and dysregulated appetite (obesity)	Q86TI0	TBCD1	TBC1 domain family member 1
Hyperphagia and dysregulated appetite (obesity)	Q9C0B1	FTO	Alpha-ketoglutarate-dependent dioxygenase FTO
Hyperphagia and dysregulated appetite (obesity)	P78415	IRX3	Iroquois-class homeodomain protein IRX-3
Hyperphagia and dysregulated appetite (obesity)	O15118	NPC1	Niemann-Pick C1 protein
Hyperphagia and dysregulated appetite (obesity)	P41161	ETV5	ETS translocation variant 5
Hyperphagia and dysregulated appetite (obesity)	Q7Z3B1	NEGR1	Neuronal growth regulator 1
Hyperphagia and dysregulated appetite (obesity)	Q5NUL3	FFAR4	Free fatty acid receptor 4
Hyperphagia and dysregulated appetite (obesity)	Q6VAB6	KSR2	Kinase suppressor of Ras 2
Hyperphagia and dysregulated appetite (obesity)	Q99932	SPAG8	Sperm-associated antigen 8
Hyperphagia and dysregulated appetite (obesity)	P04150	GCR	Glucocorticoid receptor
Hyperphagia and dysregulated appetite (obesity)	P01375	TNFA	Tumor necrosis factor (Cachectin) (TNF-alpha)

Hyperphagia and dysregulated appetite (obesity)	P40763	STAT3	Signal transducer and activator of transcription 3
Hyperphagia and dysregulated appetite (obesity)	O14543	SOCS3	Suppressor of cytokine signaling 3
Hyperphagia and dysregulated appetite (obesity)	O14920	IKKB	Inhibitor of nuclear factor kappa-B kinase subunit beta
Hyperphagia and dysregulated appetite (obesity)	O95352	ATG7	Ubiquitin-like modifier-activating enzyme
White adipose tissue formation (obesity)	P37231	PPARG	Peroxisome proliferator-activated receptor gamma
White adipose tissue formation (obesity)	P17931	LEG3	Galectin-3
White adipose tissue formation (obesity)	Q15672	TWST1	Twist-related protein 1
White adipose tissue formation (obesity)	Q9NZC2	TREM2	Triggering receptor expressed on myeloid cells 2
White adipose tissue formation (obesity)	O60240	PLIN1	Perilipin-1
Cardiomyocyte cell death (heart failure)	P35228	NOS2	Nitric oxide synthase, inducible
Cardiomyocyte cell death (heart failure)	O00165	HAX1	HCLS1-associated protein X-1

Cardiomyocyte cell death (heart failure)	P30405	PPIF	Peptidyl-prolyl cis-trans isomerase F, mitochondrial; Cyclophilin D
Cardiomyocyte cell death (heart failure)	P21796	VDAC1	Voltage-dependent anion-selective channel protein 1
Cardiomyocyte cell death (heart failure)	P45880	VDAC2	Voltage-dependent anion-selective channel protein 2
Cardiomyocyte cell death (heart failure)	Q9Y277	VDAC3	Voltage-dependent anion-selective channel protein 3
Cardiomyocyte cell death (heart failure)	P12235	ADT1	ADP/ATP translocase 1
Cardiomyocyte cell death (heart failure)	P05141	ADT2	ADP/ATP translocase 2
Cardiomyocyte cell death (heart failure)	P12236	ADT3	ADP/ATP translocase 3
Cardiomyocyte cell death (heart failure)	Q9H0C2	ADT4	ADP/ATP translocase 4
Cardiomyocyte cell death (heart failure)	P49841	GSK3B	Glycogen synthase kinase-3 beta
Cardiomyocyte cell death (heart failure)	P25445	TNR6	Tumor necrosis factor receptor superfamily member 6
Cardiomyocyte cell death (heart failure)	P48023	TNFL6	Tumor necrosis factor ligand superfamily member 6

Cardiomyocyte cell death (heart failure)	P50591	TNF10	Tumor necrosis factor ligand superfamily member 10
Cardiomyocyte cell death (heart failure)	Q13158	FADD	FAS-associated death domain protein
Cardiomyocyte cell death (heart failure)	Q15628	TRADD	Tumor necrosis factor receptor type 1-associated DEATH domain protein
Cardiomyocyte cell death (heart failure)	Q14790	CASP8	Caspase-8
Cardiomyocyte cell death (heart failure)	P42574	CASP3	Caspase-3
Cardiomyocyte cell death (heart failure)	P10415	BCL2	Apoptosis regulator Bcl-2
Cardiomyocyte cell death (heart failure)	Q07812	BAX	Apoptosis regulator BAX
Cardiomyocyte cell death (heart failure)	Q99683	M3K5	Mitogen-activated protein kinase kinase 5
Cardiomyocyte cell death (heart failure)	P31152	MAPK4	Mitogen-activated protein kinase 4
Cardiomyocyte cell death (heart failure)	Q16659	MAPK6	Mitogen-activated protein kinase 6
Cardiomyocyte cell death (heart failure)	P55957	BID	BH3-interacting domain death agonist

Cardiomyocyte cell death (heart failure)	P98170	XIAP	E3 ubiquitin-protein ligase XIAP
Cardiomyocyte cell death (heart failure)	Q13490	BIRC2	Baculoviral IAP repeat-containing protein 2
Cardiomyocyte cell death (heart failure)	O15392	BIRC5	Baculoviral IAP repeat-containing protein 5 / survivin
Cardiomyocyte cell death (heart failure)	Q9NR28	DBLOH	Diablo homolog, mitochondrial
Cardiomyocyte cell death (heart failure)	O43464	HTRA2	Serine protease HTRA2, mitochondrial
Cardiomyocyte cell death (heart failure)	Q811U4	MFN1	Mitofusin-1
Cardiomyocyte cell death (heart failure)	Q07820	MCL1	Induced myeloid leukemia cell differentiation protein Mcl-1
Cardiomyocyte cell death (heart failure)	Q92934	BAD	Bcl2-associated agonist of cell death
Cardiomyocyte cell death (heart failure)	P04637	P53	Cellular tumor antigen p53
Cardiomyocyte cell death (heart failure)	P29466	CASP1	Caspase-1
Cardiomyocyte cell death (heart failure)	P13473	LAMP2	Lysosome-associated membrane glycoprotein 2

Cardiomyocyte cell death (heart failure)	Q9H1Y0	ATG5	Autophagy protein 5
Cardiomyocyte cell death (heart failure)	O75385	ULK1	Serine/threonine-protein kinase ULK1
Cardiomyocyte cell death (heart failure)	P49815	TSC2	Tuberin
Cardiomyocyte cell death (heart failure)	Q8N122	RPTOR	Regulatory-associated protein of mTOR
Cardiomyocyte cell death (heart failure)	Q14457	BECN1	Beclin-1
Cardiomyocyte cell death (heart failure)	Q12983	BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
Cardiomyocyte cell death (heart failure)	O00429	DNM1L	Dynamin-1-like protein
Cardiomyocyte cell death (heart failure)	P12644	BMP4	Bone morphogenetic protein 4
Cardiomyocyte cell death (heart failure)	O95140	MFN2	Mitofusin-2
Heart hypertrophy (heart failure)	Q9UBK2	PRGC1	Peroxisome proliferator-activated receptor gamma coactivator 1- α
Heart hypertrophy (heart failure)	P06396	GELS	Gelsolin
Heart hypertrophy (heart failure)	P49238	CX3C1	CX3C chemokine receptor 1
Heart hypertrophy (heart failure)	P78423	X3CL1	Fractalkine

Heart hypertrophy (heart failure)	P49116	NR2C2	Nuclear receptor subfamily 2 group C member 2
Heart hypertrophy (heart failure)	P63098	CANB1	Calcineurin subunit B type 1
Heart hypertrophy (heart failure)	Q96LZ3	CANB2	Calcineurin subunit B type 2
Heart hypertrophy (heart failure)	P00533	EGFR	epidermal growth factor receptor
Heart hypertrophy (heart failure)	P09038	FGF2	Fibroblast growth factor 2 / Basic fibroblast growth factor
Heart hypertrophy (heart failure)	Q14571	ITPR2	Inositol 1,4,5-trisphosphate receptor type 2
Heart hypertrophy (heart failure)	P03956	MMP1	Matrix metalloproteinase-1
Heart hypertrophy (heart failure)	P28482	MAPK1	Mitogen-activated protein kinase 1
Heart hypertrophy (heart failure)	P27361	MAPK3	Mitogen-activated protein kinase 3
Heart hypertrophy (heart failure)	Q99836	MYD88	Myeloid differentiation primary response protein MyD88
Heart hypertrophy (heart failure)	P29474	NOS3	Nitric oxide synthase, endothelial
Heart hypertrophy (heart failure)	O95644	NFAC1	Nuclear factor of activated T-cells 1
Heart hypertrophy (heart failure)	Q13469	NFAC2	Nuclear factor of activated T-cells 2
Heart hypertrophy (heart failure)	Q12968	NFAC3	Nuclear factor of activated T-cells 3
Heart hypertrophy (heart failure)	Q14934	NFAC4	Nuclear factor of activated T-cells 4
Heart hypertrophy (heart failure)	P61296	HAND2	Heart- and neural crest derivatives-expressed protein 2
Heart hypertrophy (heart failure)	P05121	PAI1	Plasminogen activator inhibitor 1
Heart hypertrophy (heart failure)	Q15418	KS6A1	Ribosomal protein S6 kinase alpha-1 (p90RSK)

Heart hypertrophy (heart failure)	Q15349	KS6A2	Ribosomal protein S6 kinase alpha-2 (p90RSK)
Heart hypertrophy (heart failure)	P51812	KS6A3	Ribosomal protein S6 kinase alpha-3 (p90RSK)
Heart hypertrophy (heart failure)	Q08209	PP2BA	Serine/threonine-protein phosphatase 2B catalytic subunit α isoform
Heart hypertrophy (heart failure)	P16298	PP2BB	Serine/threonine-protein phosphatase 2B catalytic subunit β isoform
Heart hypertrophy (heart failure)	P48454	PP2BC	Serine/threonine-protein phosphatase 2B catalytic subunit γ isoform
Heart hypertrophy (heart failure)	Q9UBN4	TRPC4	Short transient receptor potential channel 4
Heart hypertrophy (heart failure)	P32418	NAC1	Sodium/calcium exchanger 1
Heart hypertrophy (heart failure)	P30556	AGTR1	Type-1 angiotensin II receptor
Inflammation (heart failure)	P13500	CCL2	C-C motif chemokine 2
Inflammation (heart failure)	P16581	LYAM2	E-selectin
Inflammation (heart failure)	P05362	ICAM1	Intercellular adhesion molecule 1
Inflammation (heart failure)	P01584	IL1B	Interleukin 1 beta
Inflammation (heart failure)	Q14116	IL18	Interleukin 18
Inflammation (heart failure)	P05231	IL6	Interleukin 6
Inflammation (heart failure)	P19320	VCAM1	Vascular cell adhesion protein 1
Inflammation (heart failure)	P04275	VWF	von Willebrand factor
Oxidative stress (heart failure)	Q9NSA1	FGF21	Fibroblast growth factor 21
Oxidative stress (heart failure)	P04839	CY24B	NADPH oxidase 2

Oxidative stress (heart failure)	Q9NPH5	NOX4	NADPH oxidase 4
Oxidative stress (heart failure)	Q15848	ADIPO	Adiponectin
Inefficient myocardial fuel metabolism (heart failure)	O14734	ACOT8	Acyl-coenzyme A thioesterase 8
Inefficient myocardial fuel metabolism (heart failure)	O75521	ECI2	Enoyl-CoA delta isomerase 2, mitochondrial
Inefficient myocardial fuel metabolism (heart failure)	Q03181	PPARD	Peroxisome proliferator-activated receptor delta
Inefficient myocardial fuel metabolism (heart failure)	Q8NCC3	PAG15	Group XV phospholipase A2
Inefficient myocardial fuel metabolism (heart failure)	P24752	THIL	Acetyl-CoA acetyltransferase, mitochondrial
Inefficient myocardial fuel metabolism (heart failure)	P55809	SCOT1	Succinyl-CoA:3-ketoacid coenzyme A transferase 1, mitochondrial
Inefficient myocardial fuel metabolism (heart failure)	Q02338	BDH	D-beta-hydroxybutyrate dehydrogenase, mitochondrial

Supplemental Table 2. List of primers used in this study.

Transcript	Forward primer (5' – 3')	Reverse primer (5' – 3')
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BIRC5	GCATAGGAAGCACTCCCCTG	CCTGGAAAGCTGGGACAAGT
XIAP	TATGACGCACGGATCGTTAC	CACCCTGGATAACCACTTAGC
36B4	GTTGCCTCAGTGCCTCACTC	GCAGCCGCAAATGCAGATGG

Supplemental Table 3

Description of each link depicted in Figure 2. MoA Protein A refers to the mechanism of action by which a protein engages with the next protein; the MoA Protein B, expressed in the Figure 1 with a green or red arrow. The Uniprot code column shows the annotated code of a specific protein to standardize the nomenclature. The last column shows references to support every connection. MoA = Mechanism of Action.

MoA PROTEIN A		MoA PROTEIN B		REFERENCE
Entry name	Uniprot code	Entry name	Uniprot code	
BIRC5	O15392	Heart failure		PMID: 19919994
NHE1	P19634	Heart failure		PMID: 23909633 PMID: 24080184 PMID: 23429007
NHE1	P19634	Heart failure		PMID: 22803959
NHE1	P19634	AKT1	P31749	PMID: 19028724
NHE1	P19634	AKT2	P31751	PMID: 19028724
NHE1	P19634	AKT3	Q9Y243	PMID: 19028724
MAPK3	P27361	NHE1	P19634	PMID: 11807182
MAPK3	P27361	NOS2	P35228	PMID: 16283237
MAPK3	P27361	RPTOR	Q8N122	PMID: 21071439
MAPK1	P28482	NHE1	P19634	PMID: 11807182

MAPK1	P28482	NOS2	P35228	PMID: 16283237
NOS2	P35228	Heart failure		PMID: 29311992
XIAP	P98170	Heart failure		PMID: 19919994
BIRC2	Q13490	BIRC5	O15392	PMID: 15665297
BIRC2	Q13490	XIAP	P98170	PMID: 18414036
RPTOR	Q8N122	Heart failure		PMID: 24859226
EMPAGLIFLOZIN		NHE1	P19634	Drug target
AKT1	P31749	MAPK3	P27361	KEGG: map04371
AKT2	P31751	MAPK3	P27361	KEGG: map04371
AKT3	Q9Y243	MAPK3	P27361	KEGG: map04371
AKT1	P31749	MAPK1	P28482	KEGG: map04371
AKT2	P31751	MAPK1	P28482	KEGG: map04371
AKT3	Q9Y243	MAPK1	P28482	KEGG: map04371
AKT1	P31749	NOS2	P35228	PMID: 28067899
AKT2	P31751	NOS2	P35228	PMID: 28067899
AKT3	Q9Y243	NOS2	P35228	PMID: 28067899

AKT1	P31749	BIRC2	Q13490	KEGG: map01524 PMID: 29769618
AKT2	P31751	BIRC2	Q13490	PMID: 29769618
AKT3	Q9Y243	BIRC2	Q13490	PMID: 29769618
AKT1	P31749	RPTOR	Q8N122	PMID: 21339740 PMID: 26160839 KEGG: map04211
AKT2	P31751	RPTOR	Q8N122	PMID: 21339740 PMID: 26160839 KEGG: map04211
AKT3	Q9Y243	RPTOR	Q8N122	PMID: 21339740 PMID: 26160839 KEGG: map04211
MAPK1	P28482	RPTOR	Q8N122	PMID: 21071439
MAPK1	P28482	LEP	A4D0Y8	PMID: 19688109
MAPK3	P27361	LEP	A4D0Y8	PMID: 19688109
LEP	A4D0Y8	NOS2	P35228	PMID: 19688109
CaN	Q08209	CaM	P0DP23	PMID: 22100452
CaM	P0DP23	CaMKII	Q96RR4	PMID: 14722083

NOS2	P35228	CaMKII	Q96RR4	PMID: 24498331
CaN	Q08209	Heart Failure		PMID: 15336966 PMID: 12015416 PMID: 10086361
CAMKII	Q96RR4	Heart Failure		PMID: 23877259 PMID: 21276796 PMID: 18218981

Supplemental Video 1.

The image shows an example of the training process of mathematical models by TPMS. During the training process, a constant population of mathematical solutions is optimized in successive computational cycles (new mathematical solutions are generated while the worst are removed). The models are trained with part of the training information and then evaluated using the other part, which the software never had exposure to before. The video shows the compromise between the memorization capacity (ability of the models to reproduce the information used in the training process) and the generalization capacity (ability to predict the information used during the validation process in independent sets of data) of the model solutions population.