

TABLE 1.1: heart failure exon mutations related to Phosphorylation

Exon site	Gene	Amino acid change	cDNA change	Mutation frequency	Protein annotation
1	MASP2	p.H155R	A464G	22.22%	Mannan-binding lectin serine protease 2 B chain
1*	PLA2G2A	p.H19Y	C55T	44.44%	Phospholipase A2, membrane associated (Precursor)
1	FPGTTN NI3K	p.I686T	c.T2057C	22.22%	Serine/threonine-protein kinase TNNI3K 1
1*	OBSCN	p.P1914L p.R1761H p.E1915K p.P2129R p.S2618N p.A3335V	c.C5741T c.G5282A c.G5743A c.C6386G c.G7853A c.C10004T	22.22%	protein serine/threonine kinase activity
2	PIKFYVE	p.V1902L	c.G5704C	22.22%	1-phosphatidylinositol 3-phosphate 5-kinase
2	TNS1	p.T1086A	c.A3256G	33.33%	Tensin-1, regulation of cyclin-dependent protein serine/threonine kinase activity
2*	UGT1A3	p.Q6R	c.A17G	22.22%	UDP-glucuronosyltransferase 1-3,protein kinase C binding
3*	TTN	p.M20216T p.R14917H	c.T60647C c.G44750A	44.44%	Titin, protein serine/threonine kinase activity
3*	DAG1	p.D111N	c.G331A	22.22%	negative regulation of MAPK cascade
4	ALPK1	p.T1150fs	c.3450_3451del	22.22%	protein serine/threonine kinase activity
6	SLC35B 2	p.L249V	c.C745G	22.22%	Adenosine 3'-phospho 5'-phosphosulfate transporter
6*	SLC17A 4	p.R80Q	c.G239A	22.22%	probable small intestine urate exporter, sodium:phosphate symporter activity
6	ENPP1	p.T779P	c.A2335C	22.22%	Nucleotide pyrophosphatase
6	STX7	p.A12T	c.G34A	22.22%	Syntaxin-7;endoplasmic reticulum and intracellular protein transport
6*	MAP3K 5	p.I1250V	c.A3748G	22.22%	Mitogen-activated protein kinase kinase kinase 5
6	IGF2R	p.S1194L	c.C3581T	22.22%	Cation-independent mannose-6-phosphate receptor

7	ANKRD 61	p.M37V	c.A109G	33.33%	Ankyrin repeat domain-containing protein 61 ;protein phosphorylation
9	ROR2	p.V874I	c.G2620A	22.22%	Tyrosine-protein kinase transmembrane receptor
10	KNDC1	p.M1195I	c.G3585A	22.22%	Protein very KIND, protein serine/threonine kinase activity
11	SIK3	p.D1038E	c.C3114G:	22.22%	Serine/threonine-protein kinase SIK3
12	LRRK2	p.P1446L	c.C4337T	22.22%	Leucine-rich repeat serine/threonine-protein kinase
12	SSH1	p.Q59H	c.A177T	33.33%	Protein phosphatase Slingshot homolog 1
13	LMO7D N	p.S48L	c.C143T	22.22%	LMO7 downstream neighbor protein, peptidyl-serine phosphorylation
16	SBK1	p.L104F	c.C310T	22.22%	Serine/threonine-protein kinase SBK1
17*	SMG6	p.H325R	c.A974G	22.22%	Telomerase-binding protein EST1A, regulation of dephosphorylation
18*	CDH2	p.A87T	c.G259A	22.22%	Cadherin-2 ,protein phosphatase binding
20	MYT1	p.T809S	c.C2426G	22.22%	Myelin transcription factor 1, protein serine/threonine kinase activity
22	BCR	p.E19A	c.A56C	22.22%	protein serine/threonine kinase activity
22	PPP6R2	p.D633E	c.T1899G	33.33%	Serine/threonine-protein phosphatase 6 regulatory subunit 2

TABLE 1.2: heart failure exon mutations related to immune

Exon site	Gene	Amino acid change	cDNA change	Mutation frequency	Protein annotation	GO_annotation
1	ACTL8	p.R245C	c.C733T	22.22%	Actin-like protein 8	immune system process
1*	OBSCN	p.P1914L p.R1761H p.E1915K p.P2129R p.S2618N p.A3335V	c.C5741T c.G5282A c.G5743A c.C6386G c.G7853A c.C10004T	22.22%	Obscurin	regulation of vascular permeability involved in acute inflammatory response
1*	CR2	p.T67S	c.C200G	22.22%	complement receptor type 2 isoform 1 precursor	innate immune response
5	IL7R	p.C118fs	c.355dup A	22.22%	Interleukin-7 receptor subunit alpha	immunoglobulin production
6	BTNL2	p.S334L	c.C1001T	44.44%	Butyrophilin-like protein 2	T cell mediated immunity
6	HLA-G	p.D153fs	c.459delC	22.22%	HLA-G histocompatibility antigen, class I, G, isoform CRA_b	positive regulation of T cell mediated cytotoxicity
6	HLA-A	p.R89fs p.N90fs p.V91fs	c.265_266 del c.268_269 insG c.272_273 insC	44.44%	MHC class I antigen	positive regulation of T cell mediated cytotoxicity
6	HLA-DR B5	p.A102fs	c.304_305 insGG	22.22%	major histocompatibility complex, class II, DR beta 5 precursor	immunoglobulin production involved in immunoglobulin mediated immune response
6	HLA-DR B1	p.R101fs p.Q99fs p.E98fs	c.303_304 del c.294_295 insA:c.293 dupA:	22.22%	major histocompatibility complex, class II, DR beta 1 precursor	immunoglobulin production involved in immunoglobulin mediated immune response

6	HLA-D OB	p.V244I	c.G730A	22.22%	HLA class II histocompatibility antigen, DO beta chain	immunoglobulin production involved in immunoglobulin mediated immune response
6	C6orf16 3	p.A72V	c.C215T	22.22%	Uncharacterized protein C6orf163	immune system process
6	ENPP1	p.T779P	c.A2335C	22.22%	Nucleotide pyrophosphatase	immune response
7	ZP3	p.D57N	c.G169A	22.22%	Processed zona pellucida sperm-binding protein 3	positive regulation of humoral immune response
8	SLC7A2	p.V544M	c.G1630A	55.55%	Cationic amino acid transporter 2	regulation of inflammatory response
8	ZFHX4	p.D1154V	c.A3461T	33.33%	Zinc finger homeobox protein 4	immune response-activating cell surface receptor signaling pathway
8	CSMD3	p.G2243D	c.G6728A	22.22%	CUB and sushi domain-containing protein 3	positive regulation of immune system process
9	ORM2	p.G141R	c.G421C	22.22%	Alpha-1-acid glycoprotein 2	regulation of immune system process
10	IL15RA	p.S34L	c.C101T	44.44%	Soluble interleukin-15 receptor subunit alpha	cytokine-mediated signaling pathway
11	SPON1	p.R739Q	c.G2216A	22.22%	Spondin-1	positive regulation of immune system process
11	MRGPR D	p.P192L	c.C575T	22.22%	Mas-related G-protein coupled receptor member D	immune system process
11	MYO7A	p.Y1731C	c.A5192G	22.22%	Unconventional myosin-VIIa	immune effector process
11	LAYN	p.G68V	c.G203T	22.22%	Layilin	immune system process
12	BICD1	p.L881fs	c.2643_2644del	22.22%	protein bicaudal D homolog 1 isoform 1	immune system process

14	SYNE2	p.Q3612R	c.A10835G	44.44%	Nesprin-2	immune system process
16*	NOD2	p.A661P	c.G1981C	22.22%	Nucleotide-binding oligomerization domain-containing protein 2	innate immune response in mucosa
17	MYO15A	p.G1220R	c.G3658A	33.33%	Unconventional myosin-XV	immunological synapse
17	MYO19	p.V536L	c.G1606C	22.22%	Unconventional myosin-XIX	immune response
17	SECTM1	p.V99M	c.G295A	22.22%	Secreted and transmembrane protein	immune response
17*	ACE	p.N160S	c.A479G	22.22%	Hypertrophic cardiomyopathy	Neutrophil mediated immunity
17*	CCDC40	p.D1043N	c.G3127A	22.22%	Coiled-coil domain-containing protein 40	immune system process
19	C5AR2	p.R300H	c.G899A	22.22%	C5a anaphylatoxin chemotactic receptor 2	positive regulation of immune system process
19	KIR3DL2	p.A108T	c.G322A	33.33%	Killer cell immunoglobulin-like receptor 3DL2	negative regulation of immune response
19	IL11	p.P33S	c.C97T	22.22%	Interleukin-11 (Precursor)	cytokine activity
22	MYO18B	p.G487R	c.G1459A	22.22%	Unconventional myosin-XVIIIb	immune system process
22	LGALS2	p.R49H	c.G146A	22.22%	Galectin-2	immune system process
22	APOL4	p.E108fs	c.323_324 del	22.22%	Apolipoprotein L4	inflammatory response

TABLE 2 Verification for exon mutations with heart failure disease in 1000 cases and 250 controls

Exon site	Gene	Case number	Mutation	Control number	Mutation	Mutation frequency
1	PLA2G2A	43		0		4.3%
1	OBSCN	385		0		38.5%
2	UGT1A3	32		0		3.2%
3	TTN	776		0		77.6%
3	DAG1	60		0		6%
6	SLC17A4	102		0		10.2%
6	MAP3K5	113		0		11.3%
17	SMG6	203		0		20.3%
18	CDH2	116		0		11.6%
1	OBSCN	385		0		38.5%
16	NOD2	116		0		11.6%
17	ACE	81		0		8.1%
17	CCDC40	3		0		0.3%

TABLE3: Cytokine and Chemokines detected from Plasma

Cytokine/chemokine	control(pg/ml)	Heart failure(pg/ml)
S100A12	22.96±3.35	31.74±3.12
IL-10	45.1±1.76	40.56±1.25
Osteopontin(OPN)	6736±310.9	7505±244.8
sCD163	2437±229	2872±136
sCD30 TNFRSF8	433.4±31.99	504.1±27.96
gp130 sIL-6Ra	5882±399	6719±240.7*
sTNF-R1	1143±99.12	1424±86.13*
sTNF-R2	1369±139.1	1685±110.1*
BCA-1	12.47±1.99	15.05±0.95
CTACK	1006.18±252.1	1524.20±438.32
Eotaxin-2	137.84±23.87	292.60±39.87
Fractalkine	154.89±14.41	242.45±74.80*
IL-8	4.27±0.30	6.48±0.52*
IP-10	104.17±1.63	175.41±5.69
I-TAC	6.94±1.17	10.38±2.48
MCP-1	30.91±8.41	42.08±5.20
MIG	198.55±25.46	426.82±49.21
MIP-1a	4.26±0.67	7.80±1.47*
MIP-3a	8.51±0.94	14.41±3.03
MPIF-1	201.69±44.80	307.61±65.74*
TECK	401.42±41.92	526.14±62.83